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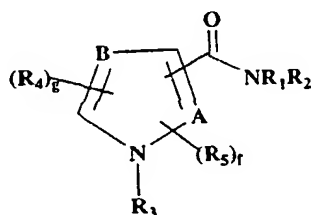
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(54) Title: CANNABINOID RECEPTOR MODULATORS, THEIR PROCESSES OF PREPARATION, AND USE OF CANNABI-
NOID RECEPTOR MODULATORS FOR TREATING RESPIRATORY AND NON-RESPIRATORY DISEASES



(I)

(57) Abstract: Use of a compound for treating a respiratory disease in a mammal wherein the compound is a cannabinoid receptor modulator is disclosed. Compounds useful as cannabinoid receptor modulators for treating respiratory and non-respiratory leukocyte-activation associated diseases comprise compounds of formula (I), in which A and B are nitrogen or carbon, provided only one of A and B is nitrogen; and R₁-R₆ are as defined in the specification, wherein R₂ with R₅ may form a ring, and/or two R₄ groups may form a six-membered aryl or heteroaryl ring, optionally having a substituent R₆ forming a ring with R₃.

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**CANNABINOID RECEPTOR MODULATORS, THEIR PROCESSES OF
PREPARATION, AND USE OF CANNABINOID RECEPTOR
MODULATORS FOR TREATING RESPIRATORY AND NON-
RESPIRATORY DISEASES**

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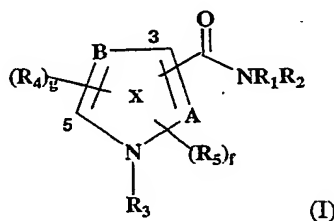
The present invention relates to compounds and compositions comprising cannabinoid receptor modulators, to processes for preparing such compounds and compositions, and to the use of cannabinoid receptor modulators in treating
10 respiratory and non-respiratory diseases.

Delta-9 THC, the principle active component of marijuana, is a member of a large family of lipophilic compounds (*i.e.*, cannabinoids) that mediate physiological and psychotropic effects including immunosuppression, analgesia, inflammation, emesis, and intraocular pressure. Cannabinoids work through selective binding to G-
15 protein coupled cannabinoid receptors. Two types of cannabinoid receptors have been cloned including CB1 (L.A. Matsuda *et al.* Nature, Vol. 346 [1990], pp. 561-564), and CB2 (S. Munro *et al.*, Nature, Vol. 365 [1993], pp. 61-65). The CB1 receptor is found mainly on cells of the central nervous system, while the CB2
20 receptor is found mainly on cells of the peripheral nervous system including cells comprising the immune system such as lymphoid cells.

Compounds that reportedly bind to the cannabinoid G-protein receptors are disclosed in European Patent Documents Nos. EP 0570920 and EP 0444451; International Publications Nos. WO 97/29079, WO 99/02499, WO 98/41519, and WO
25 9412466; U.S. Patent Nos. 4,371,720, U.S. 5,081,122, U.S. 5,292,736, and U.S. 5,013,387; and French Patent No. FR 2735774, each of which is incorporated herein by reference.

Applicants have discovered that cannabinoid receptor modulators including cannabinoid receptor agonists are useful in treating respiratory disease, such as chronic pulmonary obstructive disorder, emphysema, asthma, and bronchitis. In one aspect of the invention, there is provided the use of cannabinoid receptor modulators in treating respiratory disease in a mammal comprising administering to said mammal an effective amount of at least one cannabinoid receptor modulator. Advantageously, the cannabinoid receptor modulator for this aspect of the invention is a CB2-receptor modulator.

The present invention is also directed to compounds and pharmaceutical compositions comprising at least one cannabinoid receptor modulator, and to the use of at least one such compound in treating respiratory and non-respiratory leukocyte activation-associated disorders, wherein the compound has the formula (I):



or a pharmaceutically-acceptable salt or hydrate thereof, in which:

A and B are selected from carbon and nitrogen so that ring X defines a pyrrole, pyrazole, or imidazole ring; wherein when A is nitrogen, the group $-C(=O)NR_1R_2$ is attached to atom C-3 and R_5 does not exist; and when A is carbon, one of the group $-C(=O)NR_1R_2$ and R_5 is attached to A and the other of $-C(=O)NR_1R_2$ and R_5 is attached to atom C-3; and when B is carbon, two R_4 groups attached to B and atom C-5, respectively, optionally form a fused 6-membered aryl or 6-membered heteroaryl having one heteroatom which is nitrogen, wherein said aryl or heteroaryl has three or four groups R_6 ;

f is 0 or 1;

g is 1 or 2;

R_1 and R_2 are independently selected from hydrogen, alkyl, substituted alkyl,

heterocycloalkyl, cycloalkyl, aryl, and heterocyclo; or R_2 together with R_1 or R_5 forms a five or six membered heterocyclo;

R_3 is hydrogen, alkyl, substituted alkyl, heterocycloalkyl, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, cycloalkyl, aryl, heterocyclo, or alkoxy, or forms a heterocyclo with one of R_6 ;

R_4 is attached to atom C-5 and optionally B and at each occurrence independent of each other R_4 is selected from hydrogen, alkyl, substituted alkyl, heterocycloalkyl, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, cycloalkyl, aryl, heterocyclo, hydroxy, alkoxy, amino, aminoalkyl, cyano, halogen, alkylamide, $NR_8C(=O)R_9$, and $S(O)_uR_{10}$; or when B is carbon, optionally two R_4 groups taken together form a six-membered aryl or heteroaryl having three or four R_6 ;

R_5 is attached to A or atom C-3 and is hydrogen, alkyl, substituted alkyl, heterocycloalkyl, alkenyl, substituted alkenyl, alkoxy, aryl, or heterocyclo; or R_5 together with R_2 forms a heterocyclo;

R_6 at each occurrence independent of each other R_6 is selected from hydrogen, alkyl, substituted alkyl, heterocycloalkyl, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, aryl, cycloalkyl, substituted aryl, heterocyclo, hydroxy, alkoxy, amino, aminoalkyl, cyano, halogen, alkylamide, nitro, $NR_8C(=O)R_9$, $S(O)_uR_{10}$, $-C(=O)R_8$, $-CO_2R_8$, $-S(O)_2NR_8R_{10}$, $-C(=O)N(R_8)O(R_9)$, $-C(=O)NR_8R_9$, and $-OC(=O)R_{10}$; and/or one R_6 group together with R_3 forms a heterocyclo;

R_8 and R_9 at each occurrence independent of each other R_8 and R_9 are selected from hydrogen, alkyl, substituted alkyl, heterocycloalkyl, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, cycloalkyl, aryl, and heterocyclo; or R_8 and R_9 together form a three-to-eight membered heterocyclo; or R_8 together with R_{10} forms a three-to-eight membered heterocyclo; and

R_{10} at each occurrence independent of each other R_{10} is selected from alkyl, substituted alkyl, heterocycloalkyl, alkenyl, substituted alkenyl, alkynyl, and substituted alkynyl, or forms a heterocyclo with R_8 ; and u is 0, 1, 2 or 3.

According to another aspect of the invention, there are provided pharmaceutical compositions useful for treating respiratory disease comprising an effective amount of at least one cannabinoid receptor modulator according to formula (I) in a pharmaceutically-acceptable carrier or modulator. In a further aspect of the invention, there are provided compounds useful as cannabinoid receptor modulators and pharmaceutical compositions comprising such cannabinoid receptor modulators, wherein the compounds comprise selected compounds according to formula (I), as defined hereinafter. In a still further aspect of the invention, there is provided a process of preparing one or more intermediates to compounds of formula (I), and processes for preparing compounds of formula (I).

The following are definitions of terms used in this specification. The initial definition provided for a group or term herein applies to that group or term throughout the present specification, individually or as part of another group, unless otherwise indicated.

The term "alkyl" refers to straight or branched chain hydrocarbon groups having 1 to 12 carbon atoms, preferably 1 to 8 carbon atoms. The expression "lower alkyl" refers to alkyl groups of 1 to 4 carbon atoms.

The term "substituted alkyl" refers to an alkyl group as defined above having one, two or three substituents selected from the group consisting of halo, cyano, nitro, amino, aminoalkyl, hydroxy, OR_a, -SH, keto (=O), -C(=O)H, -CO₂H, -C(=O)(R_a), -CO₂(R_a), -SO₃H, -S(O)₀₋₂(R_a), -S(O)₂NR_aR_b, -C(=O)N(R_a)O(R_b), -C(=O)N(R_a)₂, -OC(=O)R_a, cycloalkyl, or aryl, wherein at each occurrence each of the groups R_a, R_b are independently selected from alkyl, substituted alkyl, heterocycloalkyl, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, cycloalkyl, aryl, and heterocyclo; or R_a and R_b taken together form a three-to-eight membered heterocyclo.

When the term "alkyl" is used to suffix another group, such as in "arylalkyl", "heterocycloalkyl" or cycloalkylalkyl," the term defines with more specificity at least one of the groups that a substituted alkyl will contain. In other words, in these instances the specifically-named groups are bonded directly through a substituted or unsubstituted alkyl chain as defined above. For example, an arylalkyl includes

benzyl, and a heterocycloalkyl includes ethyl-morpholino or any other straight or branched hydrocarbon chain of 1 to 12 carbon atoms having a substituted or unsubstituted heterocyclo as one of its substituents.

5 The term "alkenyl" refers to straight or branched chain hydrocarbon groups of 2 to 10, preferably 2 to 4, carbon atoms having at least one double bond. Where an alkenyl group is bonded to a nitrogen atom, it is preferred that such group not be bonded directly through a carbon bearing a double bond. When reference is made to a substituted alkenyl, the alkenyl group will have one to three substituents as recited above for alkyl groups.

10 The term "alkynyl" refers to straight or branched chain hydrocarbon groups of 2 to 10, preferably 2 to 4, carbon atoms having at least one triple bond. Where an alkynyl group is bonded to a nitrogen atom, it is preferred that such group not be bonded directly through a carbon bearing a triple bond. A "substituted alkynyl" is substituted with one to three substituents as recited above for alkyl groups.

15 The term "alkylene" refers to a chain bridge of 1 to 5 carbon atoms connected by single bonds {e.g., $-(CH_2)_x-$ wherein x is 1 to 5}, which may be branched with 1 to 3 lower alkyl groups.

The term "alkenylene" refers to a chain bridge of 2 to 5 carbon atoms having one or two double bonds connected by single bonds and which may be branched with 1 to 3 lower alkyl groups. Exemplary alkenylene groups include $-CH=CH-CH=CH-$, $-CH_2-CH=CH-$, $-CH_2-CH=CH-CH_2-$, $-C(CH_3)_2CH=CH-$ and $-CH(C_2H_5)-CH=CH-$.

The term "alkynylene" refers to a chain bridge of 2 to 5 carbon atoms that has a triple bond therein, is connected by single bonds, and may be branched with 1 to 3 lower alkyl groups. Exemplary alkynylene groups include $-C\equiv C-$, $-CH_2-C\equiv C-$, $-CH(CH_3)-C\equiv C-$ and $-C\equiv C-CH(C_2H_5)CH_2-$. When reference is made to a substituted alkylene, substituted alkenylene, or substituted alkynylene, these groups may have 1 to 3 substituents as defined above for alkyl groups.

The term "alkoxy" refers to the group OR_o , wherein the group R_o is selected from alkyl, alkenyl, alkynyl, cycloalkyl, aryl, heterocyclo, substituted alkyl, heterocycloalkyl, substituted alkenyl, or substituted alkynyl.

The term "amino" refers to -NH_2 , and the term "aminoalkyl" refers to $\text{-NR}_c\text{R}_d$, wherein R_c and R_d are independently selected from hydrogen, alkyl, substituted alkyl, heterocycloalkyl, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, cycloalkyl, aryl, heterocyclo, and -C(=O)R_e ; or R_c and R_d are taken together to form a three-to-eight membered saturated or unsaturated heterocyclo ring which may have one to three substituents as defined below for heterocyclo groups. R_e is selected from alkyl, substituted alkyl, heterocycloalkyl, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, cycloalkyl, aryl, and heterocyclo.

The term "alkylthio" refers to an alkyl or substituted alkyl group as defined above being further substituted with one of the groups -SH or -SR_s , wherein R_s is selected from alkyl, substituted alkyl, heterocycloalkyl, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, cycloalkyl, aryl, and heterocyclo.

The term "alkylamide" refers to the group $\text{-C(=O)NR}_f\text{R}_g$, wherein R_f and R_g are independently selected from hydrogen, alkyl, substituted alkyl, heterocycloalkyl, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, cycloalkyl, aryl, and heterocyclo; or R_f and R_g taken together form a three-to-eight membered heterocyclo.

The terms "ar" or "aryl" refer to aromatic cyclic groups, for example, 6 membered monocyclic, 10 membered bicyclic or 12 membered tricyclic ring systems, which contain 6 to 14 carbon atoms. Exemplary aryl groups include phenyl, naphthyl, biphenyl and anthracenyl. Whenever reference is made to an aryl group (including without limitation in these definitions and in the claims), unless otherwise specifically indicated the aryl may have one to three substituents selected from the group consisting of R_a , halo, cyano, nitro, amino, aminoalkyl, hydroxy, OR_a , -SH , -C(=O)H , $\text{-CO}_2\text{H}$, $\text{-C(=O)(R}_a\text{)}$, $\text{-CO}_2(\text{R}_a)$, $\text{-SO}_3\text{H}$, $\text{-S(O)}_{0.2}(\text{R}_a)$, $\text{-S(O)}_2\text{NR}_a\text{R}_b$, $\text{-C(=O)N(R}_a\text{)O(R}_b\text{)}$, $\text{-C(=O)N(R}_a\text{)}_2$, and -OC(=O)R_a wherein at each occurrence each of the groups R_a , R_b are independently selected from alkyl, substituted alkyl, heterocycloalkyl, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, cycloalkyl, aryl, and heterocyclo, or taken together form a substituted or unsubstituted heterocyclo.

The term "cycloalkyl" refers to fully saturated and partially unsaturated cyclic hydrocarbon groups of 3 to 12 carbon atoms. Cycloalkyl groups may be bicyclic,

e.g., such as in bicycloheptane and bicyclooctane. Whenever reference is made to a cycloalkyl (including without limitation in these definitions and in the claims), unless otherwise specifically indicated the cycloalkyl may have one to three substituents selected from the group consisting of R_a , halo, cyano, nitro, amino, aminoalkyl, hydroxy, OR_a , -SH, keto ($=O$), $-C(=O)H$, $-CO_2H$, $-C(=O)(R_a)$, $-CO_2(R_a)$, $-SO_3H$, $-S(O)_{0-2}(R_a)$, $-S(O)_2NR_aR_b$, $-C(=O)N(R_a)O(R_b)$, $-C(=O)N(R_a)_2$, and $-OC(=O)R_a$, wherein at each occurrence each of the groups R_a , R_b are independently selected from alkyl, substituted alkyl, heterocycloalkyl, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, cycloalkyl, aryl, and heterocyclo, or taken together form a heterocyclo.

The terms "halogen" and "halo" refer to fluorine, chlorine, bromine and iodine.

The terms "heterocycle", "heterocyclic" or "heterocyclo" refer to fully saturated or unsaturated, including aromatic (*i.e.* "heteroaryl") cyclic groups, for example, 4 to 7 membered monocyclic, 7 to 11 membered bicyclic, or 10 to 15 membered tricyclic ring systems, which have at least one heteroatom in at least one carbon atom-containing ring, and each ring of the heterocyclo is optionally substituted as defined below. Each ring of the heterocyclic group containing a heteroatom may have 1, 2, 3 or 4 heteroatoms selected from nitrogen atoms, oxygen atoms and/or sulfur atoms, where the nitrogen and sulfur heteroatoms may optionally be oxidized and the nitrogen heteroatoms may optionally be quaternized. The heterocyclic group may be attached at any heteroatom or carbon atom of the ring or ring system. Each ring of the heterocyclic group may have one or more (preferably one or two) substituents selected from R_a , halo, cyano, nitro, amino, aminoalkyl, hydroxy, OR_a , -SH, keto ($=O$), $-C(=O)H$, $-CO_2H$, $-C(=O)(R_a)$, $-CO_2(R_a)$, $-SO_3H$, $-S(O)_{0-2}(R_a)$, $-S(O)_2NR_aR_b$, $-C(=O)N(R_a)O(R_b)$, $-C(=O)N(R_a)_2$, $-OC(=O)R_a$, wherein at each occurrence each of the groups R_a , R_b are independently selected from alkyl, substituted alkyl, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, cycloalkyl, aryl, monocyclic heterocycloalkyl or monocyclic heterocyclo, or taken together form a heterocyclo.

Exemplary monocyclic heterocyclic groups include pyrrolidinyl, pyrrolyl, pyrazolyl, oxetanyl, pyrazolinyl, imidazolyl, imidazolinyl, imidazolidinyl, oxazolyl,

oxazolidinyl, isoxazolinyl, isoxazolyl, thiazolyl, thiadiazolyl, thiazolidinyl, isothiazolyl, isothiazolidinyl, furyl, tetrahydrofuryl, thienyl, oxadiazolyl, piperidinyl, piperazinyl, 2-oxopiperazinyl, 2-oxopiperidinyl, 2-oxopyrrolodinyl, 2-oxoazepinyl, azepinyl, 4-piperidonyl, pyridinyl, pyrazinyl, pyrimidinyl, pyridazinyl,
5 tetrahydropyranyl, morpholinyl, thiamorpholinyl, thiamorpholinyl sulfoxide, thiamorpholinyl sulfone, 1,3-dioxolane and tetrahydro-1,1-dioxothienyl, triazolyl, triazinyl, and the like. The term "diazapine" refers to a heterocyclo having at least one seven atom ring with two nitrogen atoms in said seven atom ring.

Exemplary bicyclic heterocyclic groups include indolyl, benzothiazolyl,
10 benzoxazolyl, benzodioxolyl, benzothienyl, quinuclidinyl, quinolinyl, tetra-hydroisoquinolinyl, isoquinolinyl, benzimidazolyl, benzopyranyl, indolizinyl, benzofuryl, chromonyl, coumarinyl, benzopyranyl, cinnolinyl, quinoxalinyl, indazolyl, pyrrolopyridyl, furopyridinyl (such as furo[2,3-c]pyridinyl, furo[3,2-b]pyridinyl] or furo[2,3-b]pyridinyl), dihydroisoindolyl, dihydroquinazoliny
15 (such as 3,4-dihydro-4-oxo-quinazoliny), tetrahydroquinolinyl and the like.

Exemplary tricyclic heterocyclic groups include carbazolyl, benzidolyl, phenanthrolinyl, acridinyl, phenanthridinyl, xanthenyl and the like.

The term "heteroaryl" refers to aromatic heterocyclic groups.

Exemplary heteroaryl groups include pyrrolyl, pyrazolyl, imidazolyl, oxazolyl,
20 isoxazolyl, thiazolyl, thiadiazolyl, isothiazolyl, furyl, thienyl, oxadiazolyl, pyridinyl, pyrazinyl, pyrimidinyl, pyridazinyl, triazolyl, triazinyl, and the like.

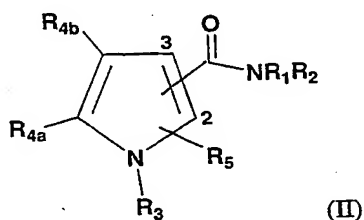
When reference is made to specifically-named heterocyclo, such as 1,2,3,4-tetrahydroquinoline, triazaspirodecane, morpholine, piperidine, pyrrolidine, thienyl, oxazole, and diazapine, and so forth, these rings may have one or more substituents as
25 defined above for heterocyclo groups.

The term "unsaturated ring" includes partially or fully unsaturated and aromatic rings. When reference is made to an unsaturated heterocyclo, this means at least one ring of the heterocyclo is unsaturated (partially or fully), *i.e.*, in a bicyclic or tricyclic heterocyclo, only one ring of the heterocyclo need be at least partially
30 unsaturated to comprise an unsaturated heterocyclo as defined herein.

Included within compounds of formula (I) are those compounds where A and B comprise carbon to define pyrrole-based compounds; where A is nitrogen and B is carbon to define pyrazole-based compounds; and where A is carbon and B is nitrogen to define imidazole-based compounds, as further defined below. One skilled in the field may make appropriate selections to provide stable compounds.

Pyrrole-Based Compounds

Compounds of formula (I) include pyrrole-based compounds useful as cannabinoid receptor modulators having formula (II), and pharmaceutically-acceptable salts thereof:



in which

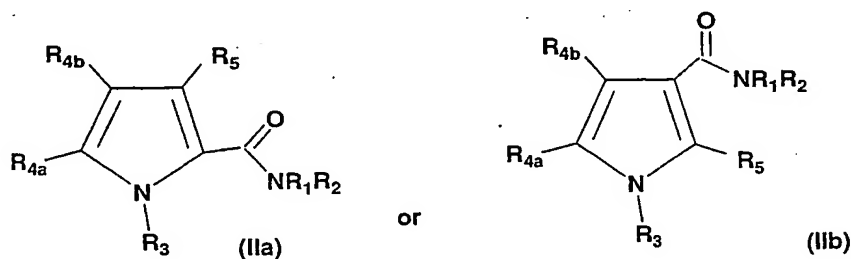
one of R_5 and the group $-C(=O)NR_1R_2$ is attached to atom C-2 and the other of R_5 and the group $-C(=O)NR_1R_2$ is attached to atom C-3 of the pyrrole ring;

R_1 and R_2 are independently selected from hydrogen, alkyl, substituted alkyl, heterocycloalkyl, cycloalkyl, aryl, and heterocyclo; or R_2 together with R_1 forms a heterocyclo; or R_2 and R_5 form a heterocyclo and R_1 is hydrogen, alkyl, substituted alkyl, heterocycloalkyl, cycloalkyl, aryl, or heterocyclo; R_3 is hydrogen, alkyl, substituted alkyl, heterocycloalkyl, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, aryl, heterocyclo, or alkoxy, or forms a heterocyclo with R_{4a} ;

R_{4a} and R_{4b} are (i) selected from hydrogen, alkyl, substituted alkyl, heterocycloalkyl, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, aryl, heterocyclo, hydroxy, alkoxy, amino, aminoalkyl, cyano, halogen, alkylamide, $NR_8C(=O)R_9$, and $S(O)_vR_{10}$; or (ii) taken together form a fused six-membered aryl or heteroaryl having three or four R_6 ;

- R₅ is hydrogen, alkyl, substituted alkyl, heterocycloalkyl, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, alkoxy, aryl, or heterocyclo; or R₅ is taken together with R₂ to form a heterocyclo;
- R₆ at each occurrence is selected independently of each other R₆ from hydrogen, alkyl, substituted alkyl, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, aryl, cycloalkyl, substituted aryl, heterocyclo, hydroxy, alkoxy, amino, aminoalkyl, cyano, halogen, alkylamide, nitro, NR₈C(=O)R₉, S(O)_uR₁₀, -C(=O)R₈, -CO₂R₈, -S(O)₂NR₈R₁₀, -C(=O)N(R₈)O(R₉), -C(=O)NR₈R₉, and -OC(=O)R₁₀; or one group R₆ forms a heterocyclo with R₃ and each other R₆ is selected from hydrogen, alkyl, substituted alkyl, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, aryl, cycloalkyl, substituted aryl, heterocyclo, hydroxy, alkoxy, amino, aminoalkyl, cyano, halogen, alkylamide, nitro, NR₈C(=O)R₉, S(O)_uR₁₀, -C(=O)R₈, -CO₂R₈, -S(O)₂NR₈R₁₀, -C(=O)N(R₈)O(R₉), -C(=O)NR₈R₉, and -OC(=O)R₁₀;
- R₈ and R₉ at each occurrence independent of each other R₈ and R₉ are selected from hydrogen, alkyl, substituted alkyl, heterocycloalkyl, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, cycloalkyl, aryl, and heterocyclo; or R₈ and R₉ taken together form a three-to-eight membered heterocyclo; or R₈ together with R₁₀ forms a three-to-eight membered heterocyclo; and
- R₁₀ at each occurrence independent of each other R₁₀ is selected from alkyl, substituted alkyl, heterocycloalkyl, alkenyl, substituted alkenyl, alkynyl, and substituted alkynyl, or forms a heterocyclo with R₈, and *u* is 0, 1, 2 or 3.

Accordingly, included within compounds of formula (II) are cannabinoid receptor modulators comprising 2-carboxamide and 3-carboxamide pyrroles, *e.g.*, compounds having formula (IIa) or (IIb), and pharmaceutically-acceptable salts thereof:

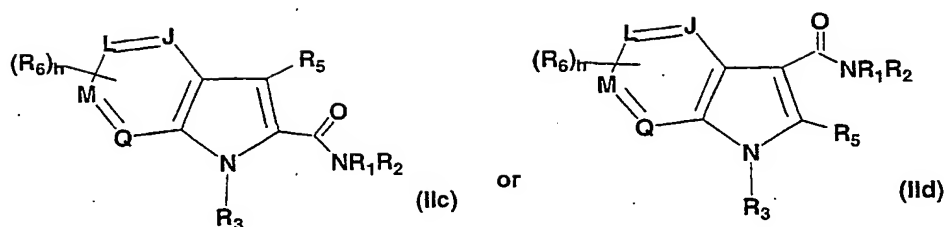


wherein

- R_1 and R_2 are (i) independently selected from hydrogen, alkyl, substituted alkyl, heterocycloalkyl, aryl, cycloalkyl, and heterocyclo; or (ii) taken together form a heterocyclo that is unsaturated or selected from optionally-substituted 1,2,3,4-tetrahydroquinoline, triazaspirodecane, morpholine, piperidine, pyrrolidine, and diazapine;
- R_3 is hydrogen, alkyl, substituted alkyl, heterocycloalkyl, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, aryl, or heterocyclo;
- R_{4a} and R_{4b} are independently selected from hydrogen, alkyl, substituted alkyl, heterocycloalkyl, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, aryl, heterocyclo, hydroxy, alkoxy, amino, aminoalkyl, cyano, halogen, alkylamide, $NR_8C(=O)R_9$, and $S(O)_uR_{10}$;
- R_5 is hydrogen, alkyl, substituted alkyl, heterocycloalkyl, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, alkoxy, aryl, or heterocyclo; and
- R_{10} is alkyl, substituted alkyl, heterocycloalkyl, alkenyl, substituted alkenyl, alkynyl, or substituted alkynyl, and u is 0, 1, 2 or 3.

With respect to compounds of formulae (IIa) and (IIb) useful as cannabinoid receptor modulators, 3-carboxamide pyrroles are preferred. Additionally, advantageously R_1 is alkyl, substituted alkyl, heterocycloalkyl, aryl, cycloalkyl, or heterocyclo, and R_2 is hydrogen or C_{1-3} alkyl. R_3 is preferably heterocycloalkyl (particularly morpholinylethyl), and R_{4a} and R_{4b} are hydrogen, halogen, lower alkyl, or alkoxy (more preferably C_{1-5} alkoxy, OPh, or OBn). Also preferred are those carboxamide pyrroles where R_1 is $-CHR_{17}R_{18}$, wherein R_{17} and R_{18} are selected from substituted alkyl, $-CO_2$ (alkyl), and alkylamide, or where R_{17} and R_{18} together form a cycloalkyl, an aryl, or a heterocyclo wherein said heterocyclo has sulfur or at least one of nitrogen and oxygen as its heteroatom(s).

Further included within compounds of formula (II) are compounds comprising bicyclic or tricyclic ringed systems having formula (IIc) or (IId), and pharmaceutically-acceptable salts thereof:

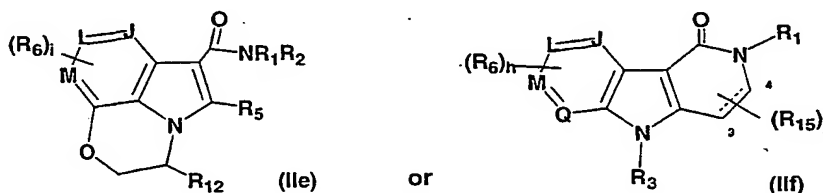


wherein J, L, M and Q are carbon or nitrogen, provided that only one of J, L, M and Q is nitrogen;

- 5 R₁, R₂, R₃, R₅ and R₆ are as defined above for compounds of formula (II), provided that when R₃ forms a ring with one of R₆, Q is carbon and R₂ is selected independently of R₅; and *h* is 3 or 4.

In compounds of formula (II), particularly (IIC) and (IID), when R₁ and R₂ together form a heterocycle ring, advantageously said ring is unsaturated or is
 10 selected from optionally-substituted 1,2,3,4-tetrahydroquinoline, triazaspirodecane, morpholine, piperidine, pyrrolidine, and diazapine. When R₁ and R₂ independently comprise heterocycle, advantageously said heterocycle has as its heteroatom or
 heteroatoms either (i) sulfur or, (ii) at least one of nitrogen and oxygen. For example, R₁ and R₂ may independently comprise pyridine, pyrazole, imidazole, tetrazole,
 15 oxazole, oxadiazole, thiophene, morpholine, and so forth. Advantageously, R₅ is not phenyl when attached to atom C-3 and at least one R₆ is alkoxy (preferably O-C₁-alkyl, OPh, or OBn), and two R₆ groups are not simultaneously selected from amino and aminoalkyl.

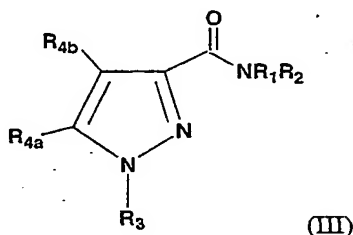
Further included within compounds of formula (IIC) and (IID) are compounds
 20 comprising tricyclic ringed systems having formula (IIe) or (IIIf), respectively, and pharmaceutically-acceptable salts thereof:



wherein J, L, M, and Q are carbon or nitrogen, provided that only one of J, L, M and Q is nitrogen; R₁, R₂, R₃, R₅, R₆, R₈, R₉ and R₁₀ are as defined above for compounds of formula (IIa) and (IIb); R₁₂ and R₁₅ selected independently of each other are hydrogen, alkyl, substituted alkyl, heterocycloalkyl, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, aryl, heterocyclo, hydroxy, alkoxy, amino, aminoalkyl, cyano, halogen, alkylamide, nitro, NR₈C(=O)R₉, S(O)_uR₁₀, keto (=O), -C(=O)R₈, -CO₂R₈, -S(O)₂NR₈R₁₀, -C(=O)N(R₈)O(R₉), -C(=O)NR₈R₉, or -OC(=O)R₁₀; *i* is 2 or 3; and *j* is 2 or 4. In compounds of formula (II), including (IIa) through (IIe), as they appear the groups J, L, M, and Q are preferably carbon; preferably R₁ is substituted alkyl and R₂ is hydrogen or C₁₋₃alkyl; R₃ and R₁₂ are -(CH₂)_n-Z or -O-(CH₂)_n-Z, wherein Z is CH₃, CO₂H, amino, aminoalkyl, alkylamide, alkoxy, heterocyclo, aryl, or cycloalkyl, and *n* is 1 or 2; R₅ and R₁₅ are hydrogen, halogen, methoxy, or lower alkyl; and each R₆ is hydrogen, alkoxy, lower alkyl, or halogen. More preferably, R₃ and R₁₂ are morpholinylC₁₋₃alkyl.

Pyrazole-Based Compounds

Included within compounds of formula (I) are pyrazole-based compounds useful as cannabinoid receptor modulators having formula (III), and pharmaceutically-acceptable salts thereof:



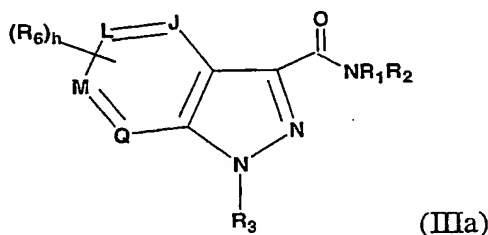
in which

- R₁ and R₂ are (i) independently selected from hydrogen, alkyl, substituted alkyl, heterocycloalkyl, cycloalkyl, aryl, and heterocyclo; or (ii) taken together form a heterocyclo;
- R₃ is hydrogen, alkyl, substituted alkyl, heterocycloalkyl, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, cycloalkyl, aryl, heterocyclo, or alkoxy; or forms a heterocyclo with R_{4a};
- R_{4a} and R_{4b} are (i) selected from hydrogen, alkyl, substituted alkyl, heterocycloalkyl, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, aryl, heterocyclo,

hydroxy, alkoxy, amino, aminoalkyl, cyano, halogen, alkylamide, $\text{NR}_8\text{C}(=\text{O})\text{R}_9$, and $\text{S}(\text{O})_u\text{R}_{10}$; or (ii) taken together form a fused six-membered aryl or heteroaryl having three or four R_6 ;

- R_6 at each occurrence is selected independently of each other R_6 from hydrogen, alkyl, substituted alkyl, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, aryl, cycloalkyl, substituted aryl, heterocyclo, hydroxy, alkoxy, amino, aminoalkyl, cyano, halogen, alkylamide, nitro, $\text{NR}_8\text{C}(=\text{O})\text{R}_9$, $\text{S}(\text{O})_u\text{R}_{10}$, $\text{C}(=\text{O})\text{R}_8$, $-\text{CO}_2\text{R}_8$, $-\text{S}(\text{O})_2\text{NR}_8\text{R}_{10}$, $-\text{C}(=\text{O})\text{N}(\text{R}_8)\text{O}(\text{R}_9)$, $-\text{C}(=\text{O})\text{NR}_8\text{R}_9$, and $-\text{OC}(=\text{O})\text{R}_{10}$; or one group R_6 forms a heterocyclo with R_3 and each other R_6 is selected from hydrogen, alkyl, substituted alkyl, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, aryl, cycloalkyl, substituted aryl, heterocyclo, hydroxy, alkoxy, amino, aminoalkyl, cyano, halogen, alkylamide, nitro, $\text{NR}_8\text{C}(=\text{O})\text{R}_9$, $\text{S}(\text{O})_u\text{R}_{10}$, $-\text{C}(=\text{O})\text{R}_8$, $-\text{CO}_2\text{R}_8$, $-\text{S}(\text{O})_2\text{NR}_8\text{R}_{10}$, $-\text{C}(=\text{O})\text{N}(\text{R}_8)\text{O}(\text{R}_9)$, $-\text{C}(=\text{O})\text{NR}_8\text{R}_9$, and $-\text{OC}(=\text{O})\text{R}_{10}$;
- R_8 and R_9 at each occurrence independent of each other are selected from hydrogen, alkyl, substituted alkyl, heterocycloalkyl, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, cycloalkyl, aryl, and heterocyclo; or R_8 and R_9 taken together form a three-to-eight membered heterocyclo; or R_8 together with R_{10} forms a three-to-eight membered heterocyclo; and
- R_{10} is selected from alkyl, substituted alkyl, heterocycloalkyl, alkenyl, substituted alkenyl, alkynyl, and substituted alkynyl, and u is 0, 1, 2 or 3.

Included within compounds of formula (III) are compounds comprising bicyclic ringed systems having formula (IIIa):

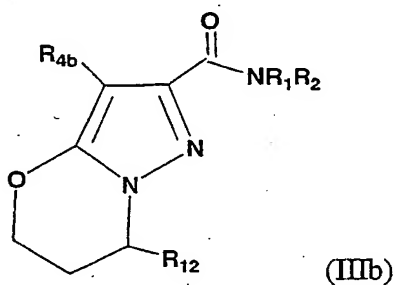


wherein J, L, M and Q are carbon or nitrogen provided that only one of J, L, M and Q is nitrogen; R_1 , R_2 , R_8 , R_9 , and R_{10} are as defined above for compounds of

formula (III); R_3 is hydrogen, alkyl, substituted alkyl, heterocycloalkyl, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, aryl, heterocyclo, or alkoxy; R_6 at each occurrence is selected independently of each other R_6 from hydrogen, alkyl, substituted alkyl, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, aryl, cycloalkyl, substituted aryl, heterocyclo, hydroxy, alkoxy, amino, aminoalkyl, cyano, halogen, alkylamide, nitro, $NR_8C(=O)R_9$, $S(O)_uR_{10}$, $-C(=O)R_8$, $-CO_2R_8$, $-S(O)_2NR_8R_{10}$, $-C(=O)N(R_8)O(R_9)$, $-C(=O)NR_8R_9$, and $-OC(=O)R_{10}$; and h is 3 or 4.

Advantageously, in compounds of formula (IIIa), J, L, M, and Q are carbon. In compounds of formula (III) and (IIIa), when R_1 and R_2 together form a heterocyclo ring, advantageously said ring is unsaturated or is selected from optionally-substituted 1,2,3,4-tetrahydroquinoline, triazaspirodecane, morpholine, piperidine, pyrrolidine, and diazapine; when R_1 and R_2 independently comprise heterocyclo, said heterocyclo has as its heteroatom or heteroatoms either (i) sulfur or, (ii) at least one of nitrogen and oxygen; and two R_6 groups are not simultaneously selected from amino and amino alkyl. Preferably, R_1 is substituted alkyl, and R_2 is hydrogen or C_{1-3} alkyl; R_3 is morpholinyl C_{1-3} alkyl; R_5 and R_{15} are hydrogen, halogen, methoxy, or lower alkyl; and each R_6 is selected from hydrogen, alkoxy, lower alkyl, or halogen.

Also included within compounds of formula (III) are compounds comprising bicyclic ringed systems having formula (IIIb):



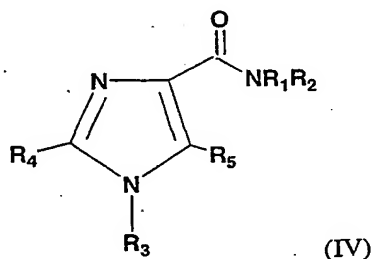
wherein R_1 , R_2 , R_{4b} , R_8 , R_9 , and R_{10} are as defined above for compounds of formula (III); and R_{12} is selected from hydrogen, alkyl, substituted alkyl, heterocycloalkyl, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, aryl, cycloalkyl, substituted aryl, heterocyclo, hydroxy, alkoxy, amino, aminoalkyl, cyano,

halogen, alkylamide, nitro, $\text{NR}_8\text{C}(=\text{O})\text{R}_9$, $\text{S}(\text{O})_u\text{R}_{10}$, $-\text{C}(=\text{O})\text{R}_8$, $-\text{CO}_2\text{R}_8$, $-\text{S}(\text{O})_2\text{NR}_8\text{R}_{10}$, $-\text{C}(=\text{O})\text{N}(\text{R}_8)\text{O}(\text{R}_9)$, $-\text{C}(=\text{O})\text{NR}_8\text{R}_9$, and $-\text{OC}(=\text{O})\text{R}_{10}$. Preferably, R_{12} is $(\text{CH}_2)_n\text{-Z}$, wherein Z is CH_3 , CO_2H , amino, aminoalkyl, alkylamide, alkoxy, aryl, cycloalkyl, or heterocyclo (preferably morpholiny), and n is 1 or 2.

5

Imidazole-Based Compounds

Also included within compounds of formula (I) are imidazole-based compounds having formula (IV); or pharmaceutically-acceptable salts thereof:



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in which

R_1 and R_2 are independently selected from hydrogen, alkyl, substituted alkyl, heterocycloalkyl, aryl, cycloalkyl, and heterocyclo; or taken together form a heterocyclo;

15 R_3 is hydrogen, alkyl, substituted alkyl, heterocycloalkyl, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, cycloalkyl, aryl, or heterocyclo;

R_4 is hydrogen, alkyl, substituted alkyl, heterocycloalkyl, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, aryl, heterocyclo, hydroxy, alkoxy, amino, aminoalkyl, cyano, halogen, alkylamide, $\text{NR}_8\text{C}(=\text{O})\text{R}_9$, or $\text{S}(\text{O})_u\text{R}_{10}$;

20 R_5 is hydrogen, alkyl, substituted alkyl, heterocycloalkyl, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, alkoxy, aryl, or heteroaryl; and

R_{10} is alkyl, substituted alkyl, heterocycloalkyl, alkenyl, substituted alkenyl, alkynyl, or substituted alkynyl, and u is 0, 1, 2 or 3.

25

In compounds of formula (IV), advantageously R_1 is substituted alkyl (more preferably $\text{CHR}_{17}\text{R}_{18}$, as defined herein); R_2 is hydrogen or C_{1-3} alkyl; R_3 is $-(\text{CH}_2)_n\text{-Z}$, wherein Z is CH_3 , CO_2H , amino, aminoalkyl, alkylamide, alkoxy, aryl, cycloalkyl, or

heterocyclo (preferably morpholiny), and n is 1 or 2; and R_4 and R_5 are hydrogen, halogen, methoxy, or lower alkyl.

When reference is made herein to compounds of formula (I), such reference includes compounds of formulae (II), (III) and (IV). Compounds of formula (I) include salts, prodrugs and solvates. The term "salt(s)" as employed herein denotes acidic and/or basic salts formed with inorganic and/or organic acids and bases. Zwitterions (internal or inner salts) are included within the term "salt(s)" as used herein (and may be formed, for example, where the R substituents comprise an acid moiety such as a carboxyl group). Also included herein are quaternary ammonium salts such as alkylammonium salts. Pharmaceutically acceptable (*i.e.*, non-toxic, physiologically acceptable) salts are preferred, although other salts are contemplated as within the scope of the invention as they may be useful, for example, in isolation or purification steps employed during preparation. Salts of the compounds of the formula (I) may be formed, for example, by reacting a compound of formula (I) with an amount of acid or base, such as an equivalent amount, in a medium such as one in which the salt precipitates or in an aqueous medium followed by lyophilization.

Exemplary acid addition salts include acetates (such as those formed with acetic acid or trihaloacetic acid, for example, trifluoroacetic acid), adipates, alginates, ascorbates, aspartates, benzoates, benzenesulfonates, bisulfates, borates, butyrates, citrates, camphorates, camphorsulfonates, cyclopentanepropionates, digluconates, dodecylsulfates, ethanesulfonates, fumarates, glucoheptanoates, glycerophosphates, hemisulfates, heptanoates, hexanoates, hydrochlorides, hydrobromides, hydroiodides, 2-hydroxyethanesulfonates, lactates, maleates, methanesulfonates, 2-naphthalenesulfonates, nicotines, nitrates, oxalates, pectinates, persulfates, 3-phenylpropionates, phosphates, picrates, pivalates, propionates, salicylates, succinates, sulfates (such as those formed with sulfuric acid), sulfonates (such as those mentioned herein), tartrates, thiocyanates, toluenesulfonates, undecanoates, and the like.

Exemplary basic salts (formed, for example, where the R substituents comprise an acidic moiety such as a carboxyl group) include ammonium salts, alkali metal salts such as sodium, lithium, and potassium salts, alkaline earth metal salts such as calcium and magnesium salts, salts with organic bases (for example, organic

amines) such as benzathines, dicyclohexylamines, hydrabamines, N-methyl-D-glucamines, N-methyl-D-glucamides, t-butyl amines, and salts with amino acids such as arginine, lysine and the like. The basic nitrogen-containing groups may be quaternized with agents such as lower alkyl halides (*e.g.* methyl, ethyl, propyl, and butyl chlorides, bromides and iodides), dialkyl sulfates (*e.g.* dimethyl, diethyl, dibutyl, and diamyl sulfates), long chain halides (*e.g.* decyl, lauryl, myristyl and stearyl chlorides, bromides and iodides), aralkyl halides (*e.g.* benzyl and phenethyl bromides), and others.

Prodrugs and solvates of the compounds of the invention are also contemplated herein. The term "prodrug" as employed herein denotes a compound which, upon administration to a subject, undergoes chemical conversion by metabolic or chemical processes to yield a compound of the formula (I), or a salt and/or solvate thereof. Solvates of the compounds of formula (I) are preferably hydrates.

All stereoisomers of the present compounds, such as those which may exist due to asymmetric carbons on the R substituents of the compound of formula (I), including enantiomeric and diastereomeric forms, are contemplated within the scope of this invention. Individual stereoisomers of the compounds of the invention may, for example, be substantially free of other isomers, or may be admixed, for example, as racemates or with all other, or other selected, stereoisomers. The chiral centers of the present invention can have the S or R configuration as defined by the IUPAC 1974 Recommendations.

According to the invention, cannabinoid receptor modulators, including compounds of formula (I), are typically employed as part of a pharmaceutical composition including a pharmaceutically-acceptable carrier for treating respiratory and/or non-respiratory diseases. The pharmaceutical compositions comprising at least one cannabinoid receptor modulator for treating respiratory disease and/or comprising compounds of formula (I), may be formulated, for example, by employing conventional solid or liquid vehicles or diluents, as well as pharmaceutical additives of a type appropriate to the mode of desired administration (for example, excipients, binders, preservatives, stabilizers, flavors, etc.) according to techniques such as those well known in the art of pharmaceutical formulation.

The cannabinoid receptor modulators for treating respiratory disease and/or compounds of formula (I) may be administered by any suitable means, for example, orally, such as in the form of tablets, capsules, granules or powders; sublingually; buccally; parenterally, such as by subcutaneous, intravenous, intramuscular, or intrasternal injection or infusion techniques (*e.g.*, as sterile injectable aqueous or non-aqueous solutions or suspensions); nasally, such as by inhalation spray; topically, such as in the form of a cream or ointment; or rectally, such as in the form of suppositories; and in dosage unit formulations containing non-toxic, pharmaceutically-acceptable vehicles or diluents. The cannabinoid receptor modulators may, for example, be administered in a form suitable for immediate release or extended release. Immediate release or extended release may be achieved by the use of suitable pharmaceutical compositions comprising the cannabinoid receptor modulators, or, particularly in the case of extended release, by the use of devices such as subcutaneous implants or osmotic pumps. The cannabinoid receptor modulators may also be administered in the form of liposomes.

Exemplary compositions for oral administration include suspensions which may contain, for example, microcrystalline cellulose for imparting bulk, alginic acid or sodium alginate as a suspending agent, methylcellulose as a viscosity enhancer, and sweeteners or flavoring agents such as those known in the art; and immediate release tablets which may contain, for example, microcrystalline cellulose, dicalcium phosphate, starch, magnesium stearate and/or lactose and/or other excipients, binders, extenders, disintegrants, diluents and lubricants such as those known in the art. The cannabinoid receptor modulators, including those for treating respiratory disease and/or compounds of formula (I), may also be delivered through the oral cavity by sublingual and/or buccal administration. Molded tablets, compressed tablets or freeze-dried tablets are exemplary forms which may be used. Exemplary compositions include those formulating the cannabinoid receptor modulators with fast dissolving diluents such as mannitol, lactose, sucrose and/or cyclodextrins. Also included in such formulations may be high molecular weight excipients such as celluloses (avicel) or polyethylene glycols (PEG). Such formulations may also include an excipient to aid mucosal adhesion such as hydroxy propyl cellulose (HPC), hydroxy propyl methyl cellulose (HPMC), sodium carboxy methyl cellulose (SCMC),

maleic anhydride copolymer (*e.g.*, Gantrez), and agents to control release such as polyacrylic copolymer (*e.g.*, Carbopol 934). Lubricants, glidants, flavors, coloring agents and stabilizers may also be added for ease of fabrication and use.

Exemplary compositions for nasal aerosol or inhalation administration include solutions in saline which may contain, for example, benzyl alcohol or other suitable preservatives, absorption promoters to enhance bioavailability, and/or other solubilizing or dispersing agents such as those known in the art.

Exemplary compositions for parenteral administration include injectable solutions or suspensions which may contain, for example, suitable non-toxic, parenterally acceptable diluents or solvents, such as mannitol, 1,3-butanediol, water, Ringer's solution, an isotonic sodium chloride solution, or other suitable dispersing or wetting and suspending agents, including synthetic mono- or diglycerides, and fatty acids, including oleic acid.

Exemplary compositions for rectal administration include suppositories which may contain, for example, a suitable non-irritating excipient, such as cocoa butter, synthetic glyceride esters or polyethylene glycols, which are solid at ordinary temperatures, but liquefy and/or dissolve in the rectal cavity to release the drug.

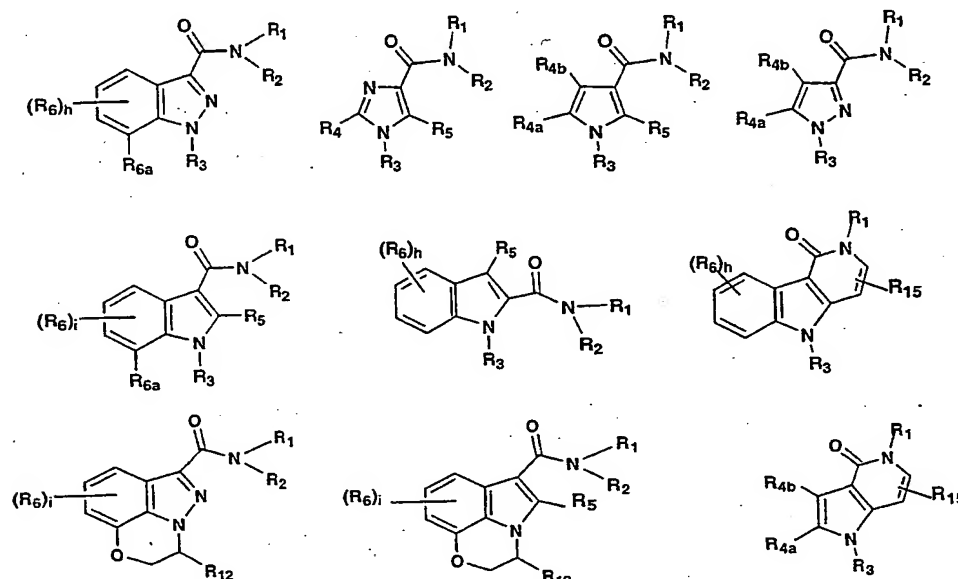
Exemplary compositions for topical administration include a topical carrier such as Plastibase (mineral oil gelled with polyethylene).

The effective amount of a compound employed in the present invention may be determined by one of ordinary skill in the art, and includes exemplary dosage amounts for an adult human of from about 0.1 to 100 mg/kg of body weight of active compound per day, which may be administered in a single dose or in the form of individual divided doses, such as from 1 to 4 times per day. It will be understood that the specific dose level and frequency of dosage for any particular subject may be varied and will depend upon a variety of factors including the activity of the specific compound employed, the metabolic stability and length of action of that compound, the species, age, body weight, general health, sex and diet of the subject, the mode and time of administration, rate of excretion, drug combination, and severity of the particular condition. Preferred subjects for treatment include animals, most preferably mammalian species such as humans, and domestic animals such as dogs, cats and the

like, subject to inflammatory, immunological, or respiratory cell-associated diseases and disorders:

Preferred Compounds

5 Particularly preferred compounds of the invention are compounds of formula (I) represented by the following structures:



10

wherein:

R_1 and R_2 are independently selected from hydrogen, alkyl, substituted alkyl, heterocycloalkyl, cycloalkyl, aryl, or heterocyclo having at its heteroatom or heteratoms either sulfur or at least one of nitrogen and oxygen; or taken together form a heterocyclo that is unsaturated or selected from optionally-substituted 1,2,3,4-tetrahydroquinoline, triazaspirodecane, morpholine, piperidine, pyrrolidine, and diazapine;

R_3 and R_{12} are $-(CH_2)_n-Z$ or $-O-(CH_2)_n-Z$;

R_4 , R_{4a} , R_{4b} and R_6 at each occurrence are selected from hydrogen, halogen, C_{1-6} alkyl, cyano, nitro, hydroxy, alkoxy, and phenyl;

20

R_5 is hydrogen, methyl, or ethyl;

R_{6a} is hydrogen or OR_8 , wherein R_8 is hydrogen, C_{1-6} alkyl, aryl, or arylalkyl;

R_{15} is hydrogen, halogen, or alkyl;

Z is CH₃, CO₂H, amino, aminoalkyl, alkylamide, alkoxy, heterocyclo, aryl, or cycloalkyl,

h is 4;

i is 3; and

5 *n* is 1 or 2.

More preferred compounds are those represented by the above-referenced structures, wherein

10 R₁ is substituted alkyl or forms a heterocyclo with R₂ that is unsaturated or selected from optionally-substituted 1,2,3,4-tetrahydroquinoline, triazaspirodecane, morpholine, piperidine, pyrrolidine, and diazapine;

R₂ is hydrogen, methyl, ethyl, or propyl, or forms a heterocyclo with R₁ that is unsaturated or selected from optionally-substituted 1,2,3,4-
15 tetrahydroquinoline, triazaspirodecane, morpholine, piperidine, pyrrolidine, and diazapine;

R₃ and R₁₂ are -(CH₂)_{*n*}-Z;

R₄, R_{4a}, R_{4b} and R₆ at each occurrence are selected from hydrogen, halogen, C₁₋₄alkyl, hydroxy, and alkoxy;

20 R₅ is hydrogen or methyl;

R_{6a} is hydrogen or OR₈, wherein R₈ is hydrogen, C₁₋₆alkyl, aryl, or arylalkyl;

R₁₅ is hydrogen, halogen, or C₁₋₂alkyl;

Z is heterocyclo;

n is 1 or 2;

25 *h* is 4; and

i is 3.

Further preferred compounds are those represented by the above-preferred structures, wherein

30 R₁ is -CHR₁₇R₁₈;

R₂ is hydrogen or methyl;

R₃ and R₁₂ are (CH₂)_{*n*}-morpholinyl;

- R_4 , R_{4a} , R_{4b} and R_6 at each occurrence are selected from hydrogen, C_{1-4} alkyl, hydroxy, and alkoxy;
- R_5 is hydrogen or methyl;
- R_{6a} is hydrogen or OR_8 , wherein R_8 is hydrogen, C_{1-5} alkyl, phenyl, or benzyl;
- 5 R_{15} is hydrogen, halogen, or C_{1-4} alkyl;
- R_{17} and R_{18} are (i) selected independently from hydrogen and $-(CH_2)_s-(CR_{21}R_{22})_v-(CH_2)_t-W$; or (ii) R_{17} and R_{18} together form cycloalkyl, aryl, or heterocyclo having as its heteroatom or heteroatoms sulfur or at least one of oxygen and nitrogen;
- 10 W at each occurrence is selected independently from CH_3 , alkylamide, aminoalkyl, alkylthio, alkoxy, hydroxy, cyano, $-CO_2R_{19}$, $-C(=O)R_{19}$, $-C(=O)N(R_{19})O(R_{20})$, $-NR_{19}(C=O)R_{20}$, aryl, cycloalkyl, and heterocyclo having as its heteroatom or heteroatoms sulfur or at least one of oxygen and nitrogen;
- R_{19} and R_{20} are selected from hydrogen, alkyl, substituted alkyl, heterocycloalkyl,
- 15 alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, cycloalkyl, aryl, and heterocyclo;
- R_{21} and R_{22} are hydrogen, alkyl, hydroxy, or hydroxyalkyl;
- h is 4;
- i is 3;
- 20 n is 1 or 2;
- s and t are 0, 1 or 2; and
- v is 0 or 1.

- Also preferred are compounds as immediately defined above where R_{17} and
- 25 R_{18} are (i) $-(CH_2)_s-W$, wherein W at each occurrence is selected from $-CH_3$, C_{1-4} alkylthio, C_{1-4} alkoxy, hydroxy, $-CO_2H$, $-CO_2C_{1-4}$ alkyl, $-C(=O)N(C_{1-4}alkyl)_2$, $-C(=O)NH(C_{1-4}alkyl)$, $-C(=O)NH(cycloalkyl)$, $-C(=O)H$, $-C(=O)NH_2$, $-C(=O)C_{1-4}alkyl$, $-C(=O)N(C_{1-4}alkyl)O(C_{1-4}alkyl)$, $-NH(C=O)C_{1-4}alkyl$, $-N(C_{1-4}alkyl)(aryl)$, $-NH(C=O)aryl$, phenyl, imidazole, biphenyl, pyridine, pyrrolidine, thiophene,
- 30 pyrazole, imidazole, tetrazole, oxazole, oxadiazole, and naphthyl, wherein said group W is optionally substituted with one to four groups selected from C_{1-4} alkyl, hydroxy, halogen, C_{1-4} alkoxy, trifluoromethyl, amino, acetylamino, heterocyclo, benzyl, or

aryl; or (ii) taken together form a three-to-eight membered cycloalkyl or bicycloalkyl optionally substituted with one to four groups selected from C₁₋₄alkyl, C₁₋₄alkoxy, aryl, cycloalkyl, and heterocyclo.

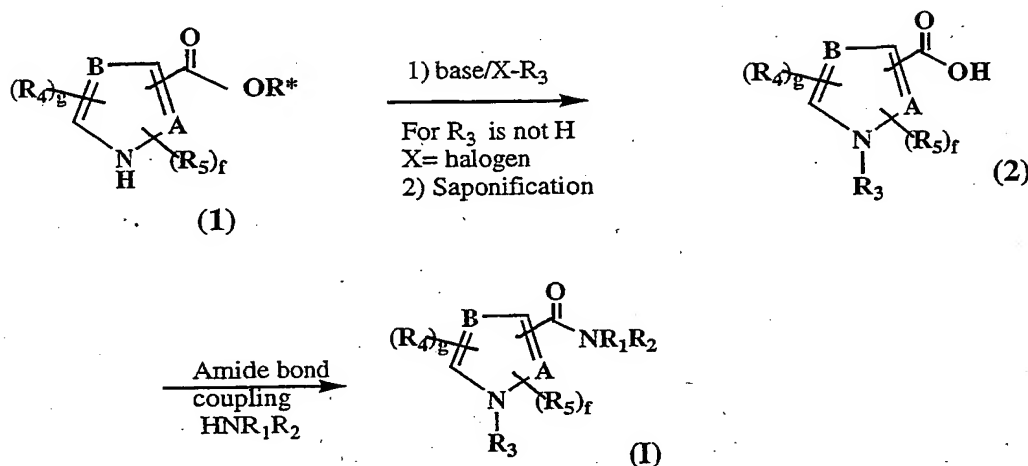
Methods of Preparation

Compounds of formula (I), cannabinoid receptor modulators illustrated in the Examples hereinafter, and intermediates for use in preparing the compounds of formula (I), may be prepared using the methods illustrated in the following Schemes A through N. Schemes A and B and G through J show schemes for preparing compounds of formula (I); schemes C through F show methods for preparing compounds useful as cannabinoid receptor modulators and as intermediates in preparing compounds of formula (I); schemes K through M describe in more detail inventive processes claimed herein for preparing compounds of formula (I); and scheme N illustrates a general procedure for Pd catalyzed indole cyclizations useful in preparing compounds of formula (I). For all of the schemes and compounds, the groups A, B, J, L, M, Q, R₁-R₆, R₁₅, and R₁₆, are as described above for a compound of formula I, unless otherwise indicated. Suitable selections may be made by one skilled in the field of appropriate groups for each of the groups X, R*, R', R'', R_a, R_b or other groups generally referenced in these schemes. Solvents, temperatures, pressures, and other reaction conditions also may readily be selected by one of ordinary skill in the art. All documents cited are incorporated herein by reference in their entirety, and abbreviations that appear hereinafter are used in these schemes for ease of reference. Starting materials are commercially available or can be readily prepared by one of ordinary skill in the art.

The methods described herein may be carried out with starting materials and/or reagents in solution or alternatively, where appropriate, with one or more starting materials or reagents bound to a solid support {see (1) Thompson, L. A. and Ellman, J. A., Chemical Reviews, 96, pp. 555-600 (1996); (2) Terrett, N. K., *et al*, Tetrahedron, 51, pp. 8135-8173 (1995); (3) Gallop, M. A. *et al*, Journal of Medicinal Chemistry, 37, 1233-1251 (1994); (4) Gordon, E. M. *et al*, Journal of Medicinal Chemistry, 37, pp. 1385-1401 (1994); (5) Balkenhohl, F., *et al*, Angewandte Chemie International Edition in English, 35, pp. 2288-2337 (1996); (6) Balkenhohl, F. *et al*,

Angewandte Chemie, 108, pp. 2436-2487 (1996); and (7) Sofia, M. J., Drugs Discovery Today, 1, pp. 27-34 (1996)}.

Scheme A



5

Starting compound (1), wherein A and B are nitrogen or carbon and R* is a carboxyl protecting group such as alkyl or arylalkyl, can be treated with a base and an alkylating agent. Exemplary bases include LDA, K₂CO₃, sodium hydride, and sodium/potassium hexamethyldisilazide, and exemplary alkylating agents include R₃X where X is a leaving group, such as a halogen or a triflate, and R₃ is preferably alkyl, arylalkyl, cycloalkylalkyl, or heterocycloalkyl. Saponification with an aqueous base such as LiOH then gives compound (2).

Compound (2) may be reacted with an amine using reaction conditions well known in the art for peptide bond synthesis {see, for example, Bodanszky and Bodanszky, The Practice of Peptide Chemistry, Springer-Verlag (1984); Bodanszky, Principles of Peptide Synthesis, Springer-Verlag (1984)} to give a compound of formula (I). Exemplary reagents for activating the carboxyl group of compound (2) for reacting with the amine include BOP chloride, BOP reagent, HATU, carbodiimides such as DCC and EDC, either alone or in combination with a hydroxybenzotriazole.

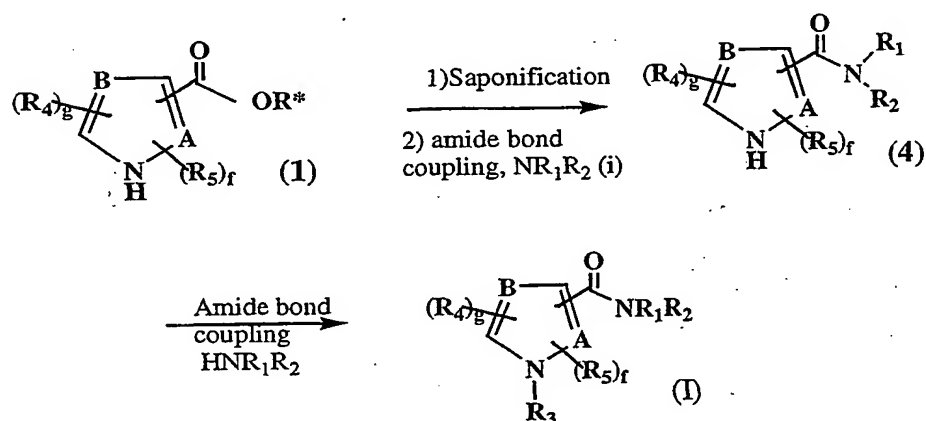
Alternatively, compound (1) can be isolated and then treated with an appropriate amine in a nonprotic solvent such as THF or DMF in the presence of base,

for example, an organic base such as TEA, DIPEA, DBU, or sodium/potassium hexamethyldisilazide, or an inorganic base such as sodium, potassium or cesium carbonate or sodium or potassium hydride.

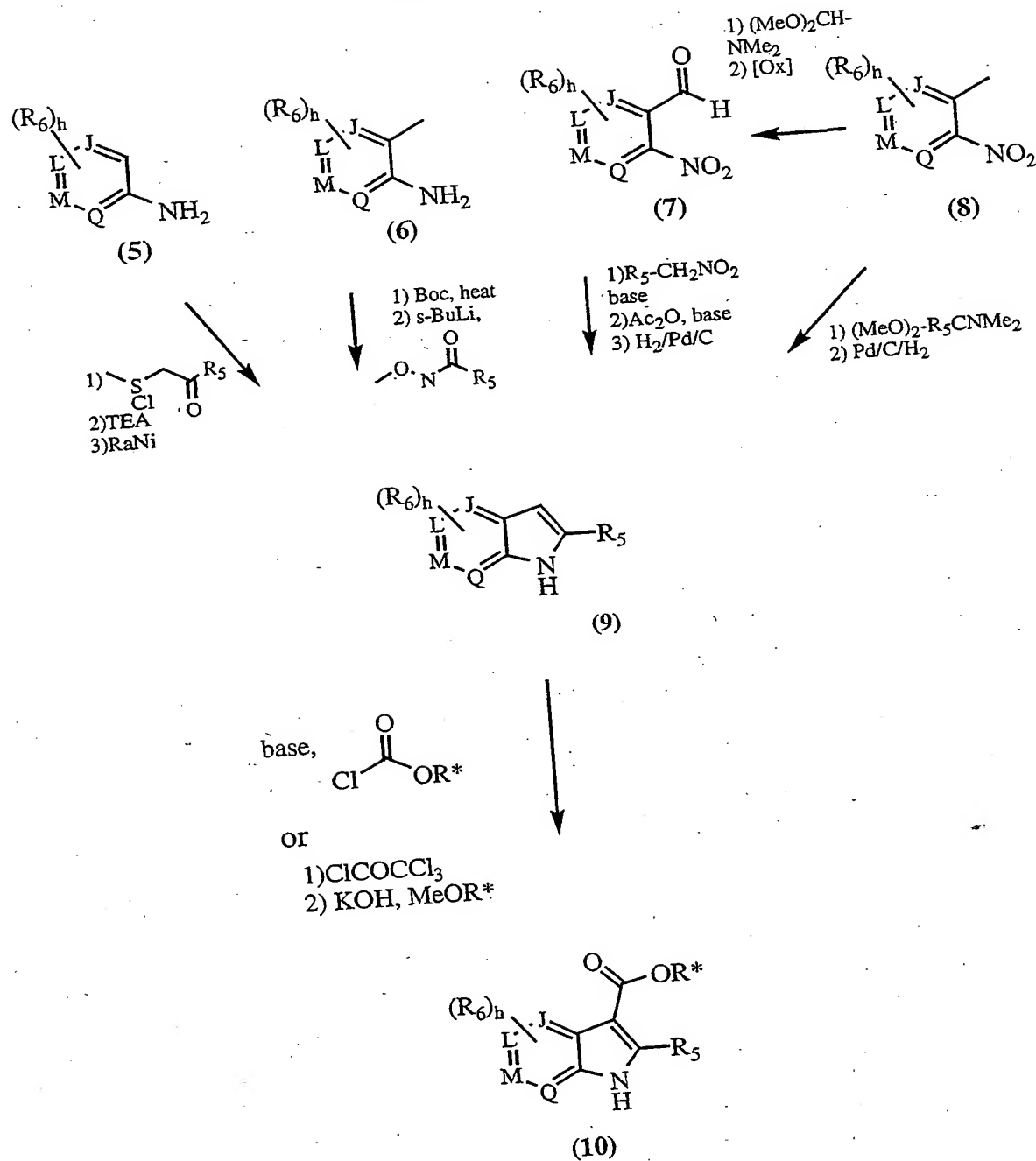
Alternatively, compound (2) may be prepared, for example, by reaction with thionyl chloride or oxalyl chloride, followed by subsequent reaction with an amine to provide a compound of formula (I).

Compound (1) is commercially available or may be readily prepared by one skilled in the field, or where A and B are carbon may be prepared as described below in Scheme J.

Scheme B



Starting compound (1) can be saponified followed by treatment with an amine under standard amide bond forming conditions (described above in Scheme A) to give compound (4). Treatment of compound (4) with a suitable base and an alkylating agent R₃X (as described above for Scheme A) gives a compound of formula (I).

Scheme C

Schemes C and D set forth methods for preparing pyrrole-based fused heterocyclic compounds (10) which may be used as starting materials (1) in Schemes A and B, *i.e.* where two R₄ groups form a fused ring. These compounds (10) may be used to form compounds of formula (I). Alternatively, compounds of formula (10) may be used in Scheme H, below, to form compounds of formula (Ib) or (Ic).

Compound (9) can be prepared alternatively from compounds (5), (6), (7) or (8) as follows:

(i) from compound (5) by treatment with beta ketochlorosulfides and a base such as TEA followed by desulfurization using raney nickel (Gassman *et al.* Journal of the American Chemical Society, Vol. 96, pp. 5512-5517 (1974);

(ii) from compound (6) by treatment with an aniline protecting group such as Boc followed by treatment with an organolithium such as sec-BuLi and an o-methyl hydroxamate;

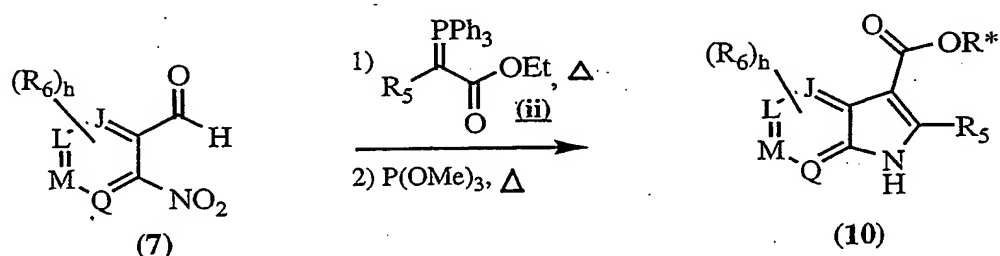
(iii) from compound (7) by treatment with a nitroalkane followed by acetylation and hydrogenation; or

(iv) from compound (8) by treatment with an alkylamide dimethyl acetal (such as N,N-dimethyl acetamide dimethyl acetal) followed by hydrogenation.

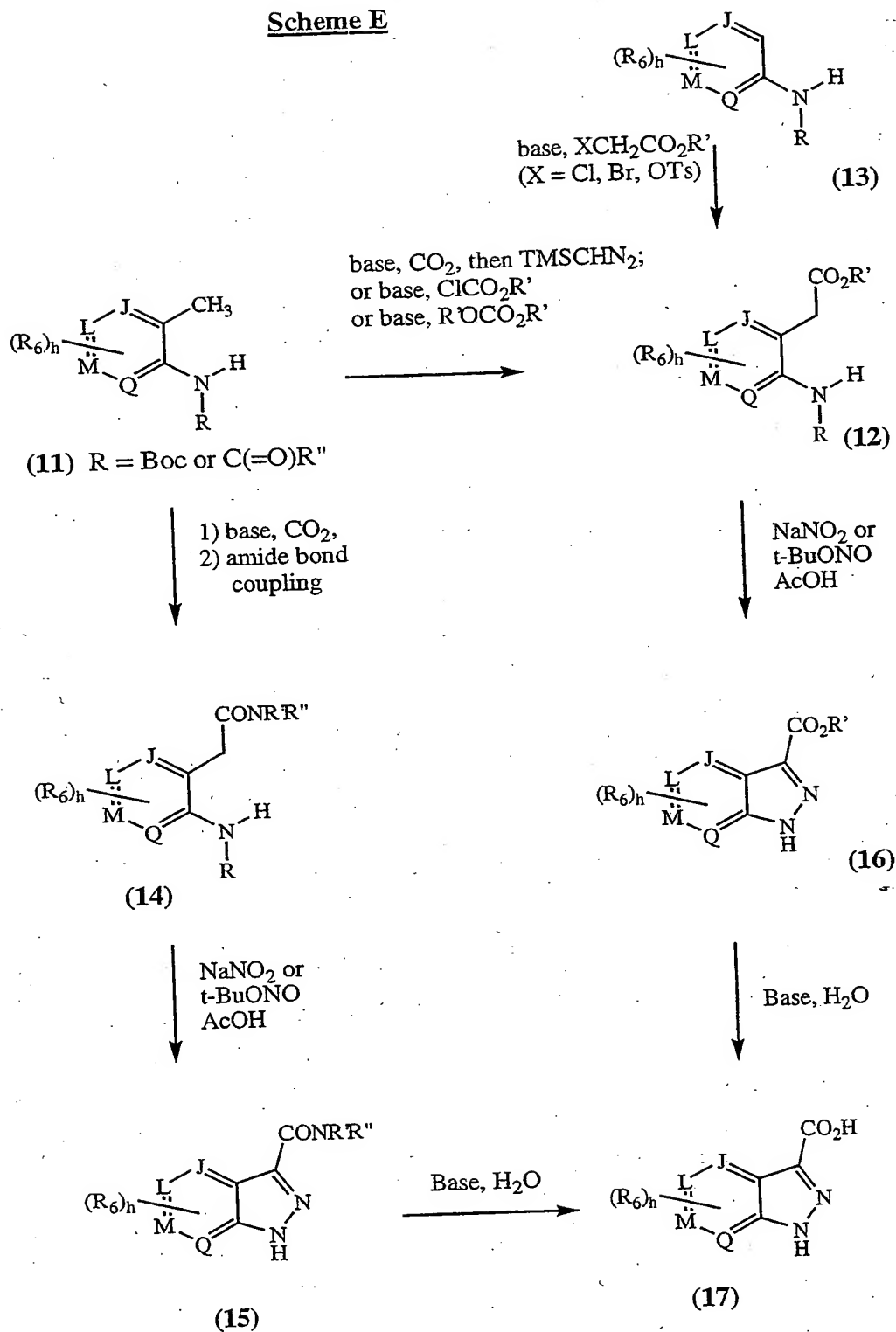
Compound (9) can be converted to compound (10) by treatment with a base such as methyl magnesium bromide and an alkyl chloroformate such as ethyl chloroformate.

Alternatively, compound (9) can be converted to compound (10) by treatment with trichloromethyl acid chloride and base such as collidine followed by conversion to an alkyl ester with an alkoxide (such as KOH) and an alcohol (such as MeOH).

Scheme D



As an alternative to scheme C, compound (10) can be prepared directly from compound (7) by treatment with a Wittig reagent such as (ii) followed by reduction/cyclization.

Scheme E

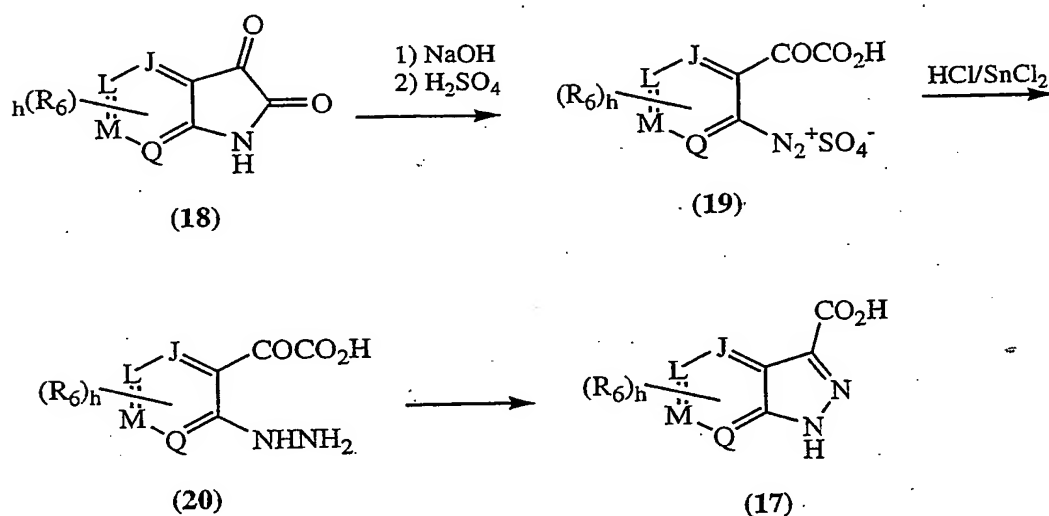
- Schemes E and F describe methods for preparing pyrazole-based compounds
 5 (17), which may be used to make compounds of formula (I) in accordance with the
 methods of Schemes A and B.

Compound (17) can be prepared from compound (11) or compound (12), *e.g.*, via base-catalyzed hydrolysis of either compound (15) or compound (16).

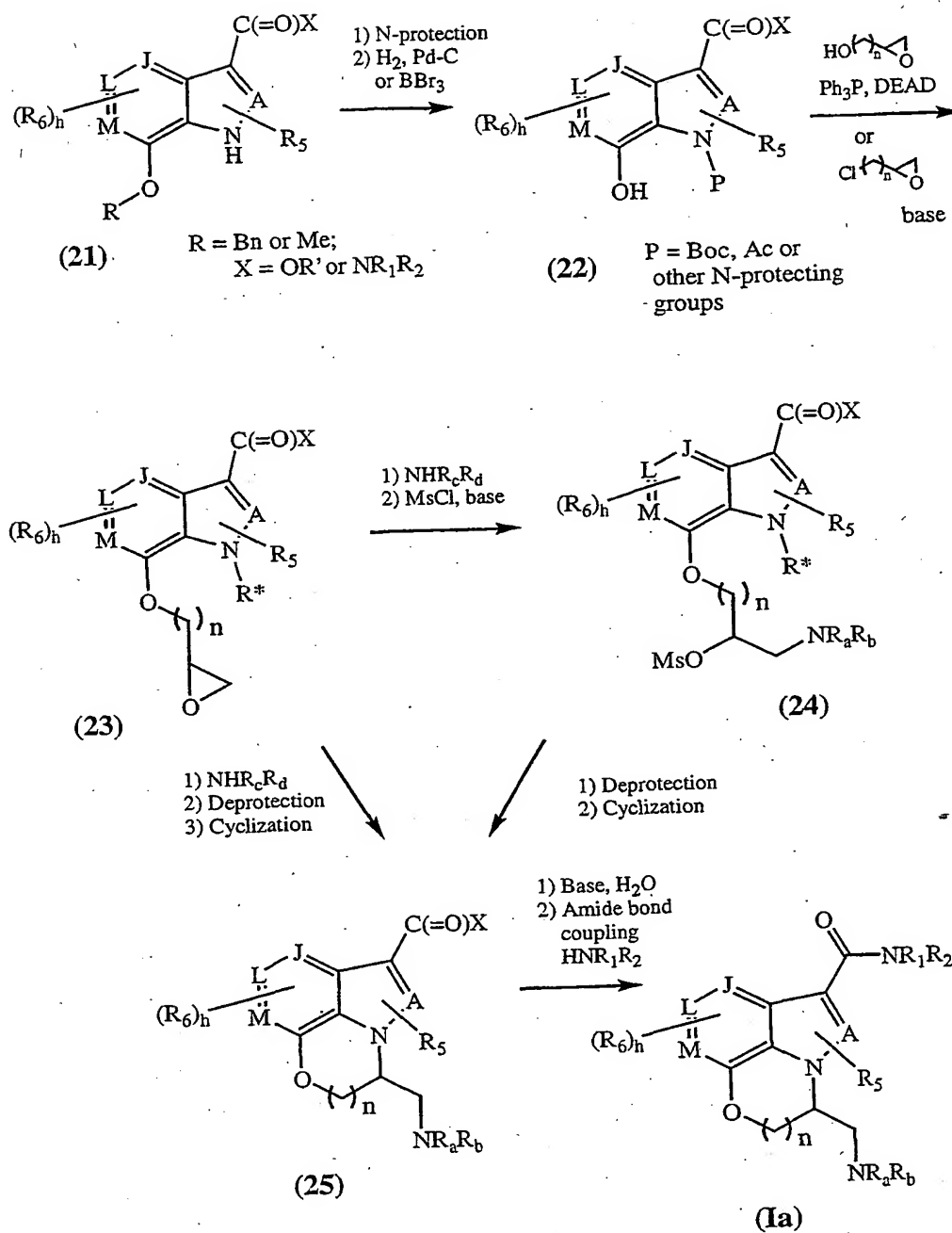
Compound (11) can be converted to compound (14) via a one-carbon extension sequence (*e.g.*, carboxylation with base and a suitable agent followed by an amide bond coupling). Compound (14) can be converted to compound (15) upon treatment with a nitroso agent, such as sodium nitrite or *tert*-butyl nitrite. Compound 12 can be converted to compound (16) under the same conditions.

Compound (12) can be prepared from compound (11) or compound (13), *i.e.*, from compound (11) via a one-carbon extension sequence (carboxylation with base and a suitable agent) or from compound (13) via a two-carbon extension sequence (alkylation with base and a suitable agent).

Scheme F



Alternatively to Scheme E, compound (17) can be prepared from compound (18) as shown in Scheme F, *i.e.*, by conversion of compound (18) to compound (19) via base-catalyzed ring opening followed by diazotization, reduction of compound (19) to compound (20), and ring closure of compound (20) to give compound (17).

Scheme G

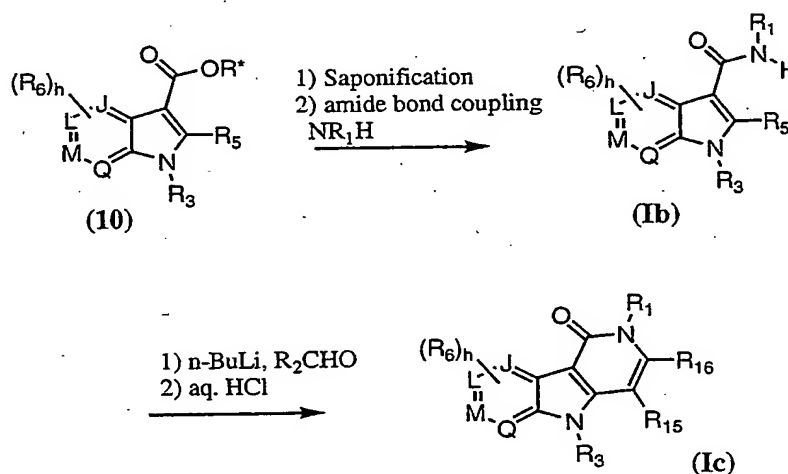
Compounds of formula (Ia) wherein A is nitrogen or carbon can be prepared from compound (21) as shown in Scheme G. Compound (21) can be N-protected and

unmasked (removal of O-benzyl or O-methyl) to give compound (22). O-alkylation of compound (22) gives compound (23).

Compound (23) can be converted to compound (25) directly via a three-step sequence: a) reaction with a suitable amine; b) removal of N-protecting group; and c) cyclization under Mitsunobu conditions. "Mitsunobu conditions" are known in the field and defined in Oyo Mitsunobu, *"The Use of Diethyl Azodicarboxylate and Triphenylphosphine in Synthesis and Transformation of Natural Products"*, Synthesis (1981), pp 1-28, which is incorporated herein by reference. Alternatively, compound (23) can be converted to compound (25) via compound (24), i.e., treatment of compound (23) with a suitable amine followed by mesylation of alcohol moiety gives compound (24), and removal of the N-protecting group of compound (24) followed by ring closure gives compound (25).

Base-catalyzed hydrolysis of compound (25) followed by an amide bond coupling reaction with a suitable amine provides compound of formula (Ia).

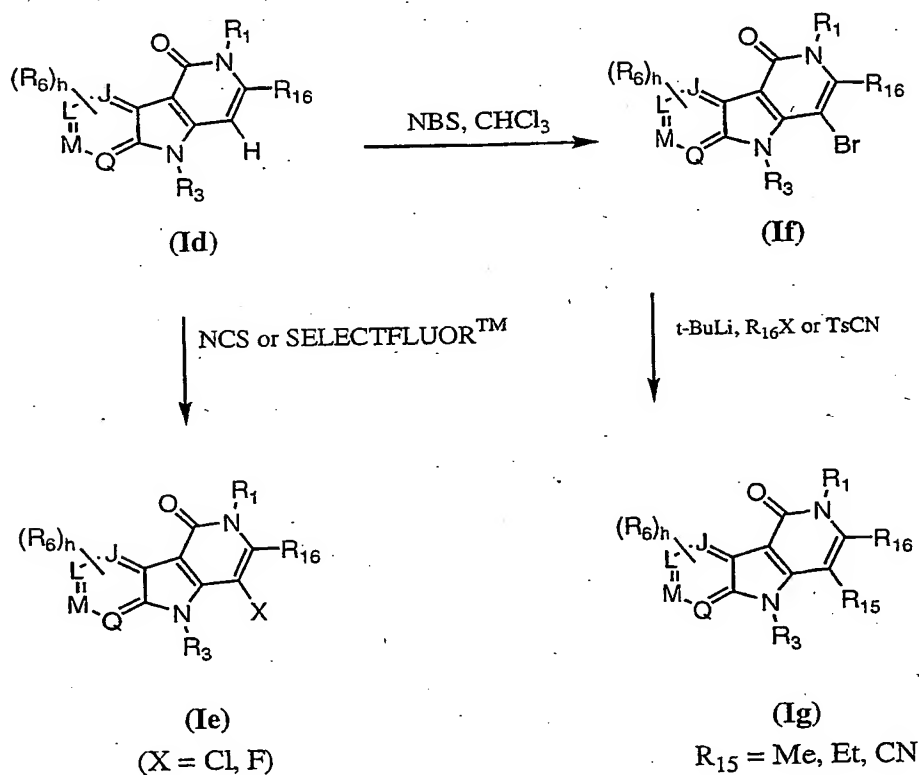
Scheme H



Scheme H describes the preparation of compounds of formula (Ic) starting with compounds of formula (10) (see Scheme C), and the methods of Schemes A and B. Compound (10) can be saponified followed by treatment with an amine under standard amide bond forming conditions (described in Scheme A) to give a compound (Ib), also a compound of formula (I). Compound (Ic) can be prepared from

compound (Ib) by treatment with an organolithium (such as n-BuLi) followed by an aldehyde derivative R_2CHO , followed by treatment with an aqueous acid such as HCl (see, e.g., Clark, R. D. *et al*, Journal of Medicinal Chemistry, Vol. 36 (1993), pp. 2645-2657) ("Clark").

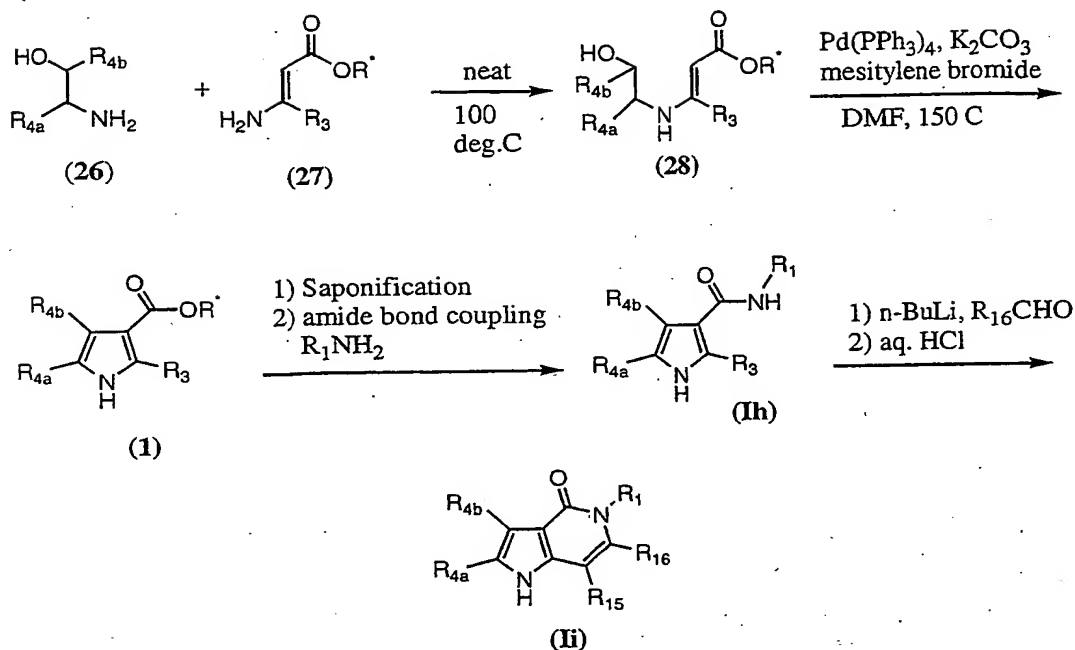
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Scheme I

Scheme I illustrates methods for preparing compounds of formulae (Ie), (If), and (Ig) from compound (Id). Compound (Ie) can be prepared from compound (Id) by treatment with NCS or SELECTFLUORTM. Compound (If) can be prepared from compound (Id) by treatment with NBS. Compound (Ig) can be prepared from compound (If) by treatment with an organolithium (such as t-BuLi) followed by treatment with an alkyl halide $R_{16}X$ or tosyl cyanide (TsCN).

Compound (Id) can be prepared from Scheme H, wherein R_{15} is hydrogen.

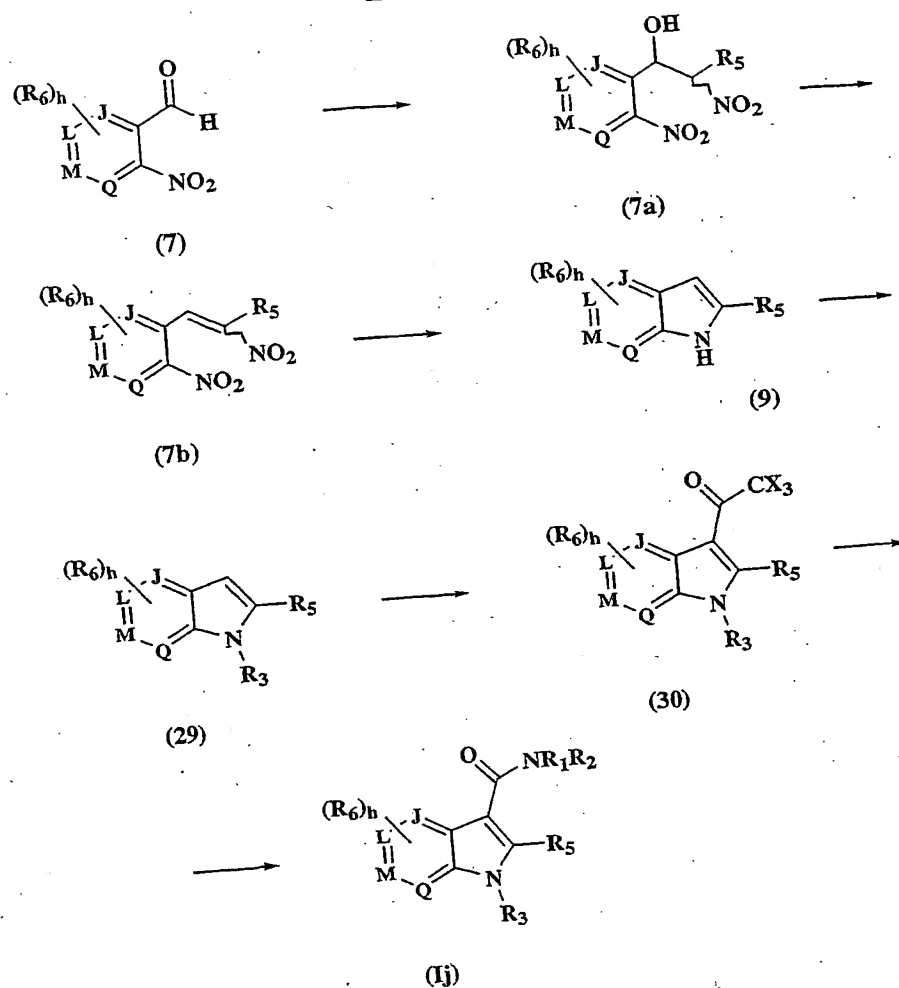
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Scheme J

Scheme J describes the formulation of compounds of formula (Ih) and (Ii).

Compound (28) can be prepared by heating a mixture compound (26) and (27).

- 5 Compound (1) can be prepared from compound (28) by treatment with a palladium catalyst such as $\text{Pd(PPh}_3\text{)}_4$, an inorganic base such as K_2CO_3 , and an aryl halide such as mesitylene bromide {see, e.g., Aoyagi, *et al.* Tetrahedron Letters, 37, 9203-9206 (1996)}. Compound (1) can be saponified followed by treatment with an amine under standard amide bond forming conditions (described above in Scheme A) to give a
- 10 compound of formula (Ih). Compound of formula (Ii) can be prepared from compound (Ih) by treatment with an organolithium (such as n-butyllithium) followed by an aldehyde derivative R_5CHO followed by treatment with an aqueous acid such as HCl (see, e.g. Clark, cited above in Scheme H).

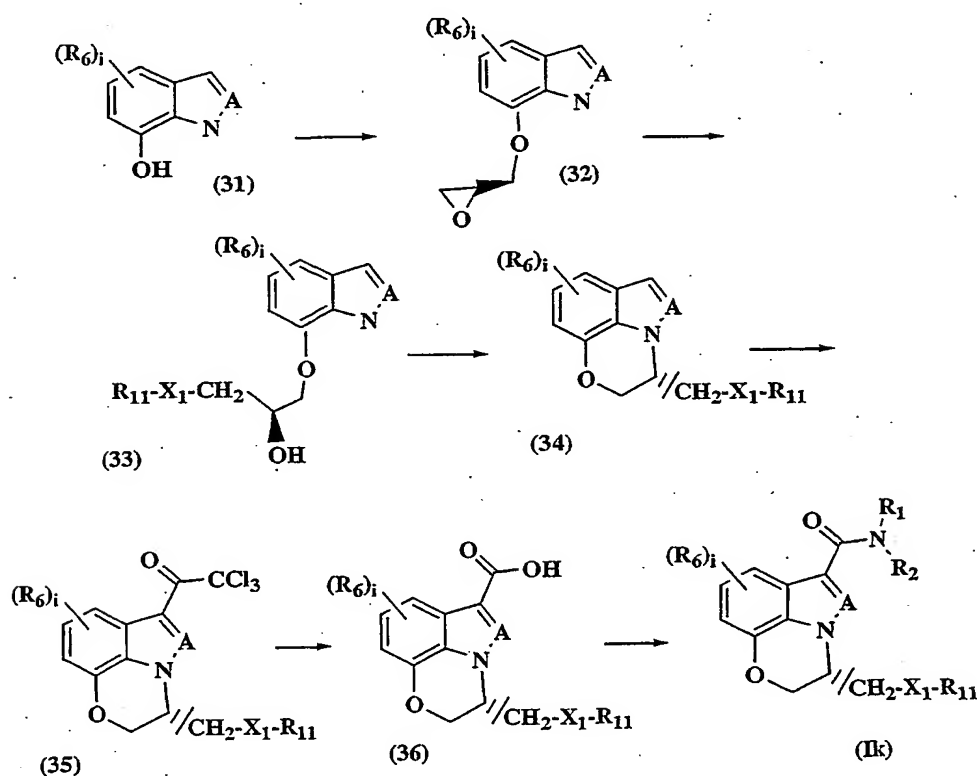
Scheme K

- 5 Scheme K describes an inventive process for making compounds of formula (Ij). Compound (7a) may be produced by reacting compound (7) (*see* Scheme C) with a nitro alkyl under appropriate conditions such as in the presence of a halide salt (e.g. potassium fluoride) and a crown ether (e.g. 18-crown-6).
- 10 Compound (7a) can be converted to a leaving group such as with acetic anhydride in sodium acetate and a fluoride-containing agent such as KF in the presence of 18-crown-6 to give a compound (7b).
- Compound (7b) can be reduced under standard hydrogenation conditions (e.g. $\text{H}_2/\text{Pd/C}$) in a suitable solvent such as $\text{EtOH}/\text{AcOH}/\text{EtOAc}$ to provide compound (9).
- 15 Compound (9) can be treated with R_3 -halide in the presence of a base such as NaOH and a suitable solvent such as DMSO to form a compound of formula (29).

Compound (29) can be treated with trihaloacetyl halide (*e.g.* where the halide is chloride) to give compound (30). In the case where R_3 does not comprise a basic substituent, a suitable base such as collidine and a suitable solvent such as DCE are necessary to give compound (30). In the case where R_3 contains a basic substituent, addition of an external base such as collidine is not needed.

Compound (30) can be treated with an appropriate amine in the presence of a suitable base to form amides of formula (Ij). Alternatively, compound (30) can be hydrolyzed to the carboxylate using a base such as NaOH followed by standard amide bond coupling methods known in the art to form compounds of formula (Ij).

Scheme L



Scheme L shows an inventive process for preparing compounds of formula (Ik), wherein A is nitrogen or CR_5 as defined herein.

The process comprises subjecting a compound (31) to alkylation (*e.g.* with (R)-(+)-glycidol under standard Mitsunobu conditions (DEAD, Ph_3P)} to give compound (32). Alternatively, compound (31) can be reacted with (R)-(-)-epichlorohydrin in base to give compound (32).

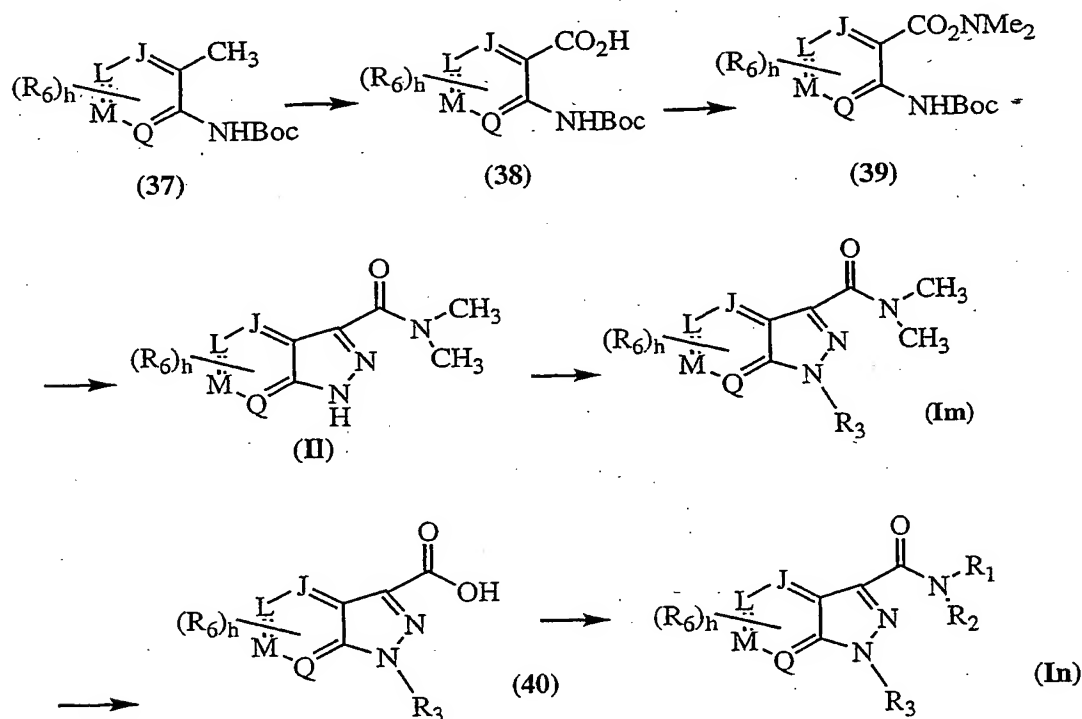
Compound (32) undergoes ring opening in the presence of a nucleophile $R_{11}-X_1$ (or $R_{11}-X_1-H$ where H is hydrogen) wherein R_{11} is selected from alkylene, substituted alkylene, alkenylene, substituted alkenylene, cycloalkyl, aryl, and heterocyclo, and X_1 (or X_1-H) is any nucleophile which can ring open an epoxide including, but not limited to alcohols, amines, thiols, azides and carbon nucleophiles to give compound (33).

Compound (33) can undergo cyclization under Mitsunobu conditions (DEAD, PPh_3) to give compound (34). Alternatively, compound (33) can be treated with a sulfonyl halide to provide a sulfonate which can cyclize to form compound (34).

Compound (34) can be treated with trihaloacetyl halide (e.g. trichloroacetyl chloride) under elevated temperatures (preferably from about 40 to 120°C) to give compound (35).

Compound (35) can be hydrolyzed under basic conditions to give compound (36). Compound (36) can be coupled to an amine using standard amide bond coupling techniques (EDC/HOBT or acid chloride) to give compounds of formula (Ik).

Scheme M



Scheme M shows an inventive process for making compounds of formulae (II) and (Im).

The process comprises reacting compound (37) with an alkyl lithium and carbon dioxide to form compound (38).

Compound (38) is reacted with a dialkyl amine under standard amide bond conditions (such as EDCI, HOBT) to form compound (39).

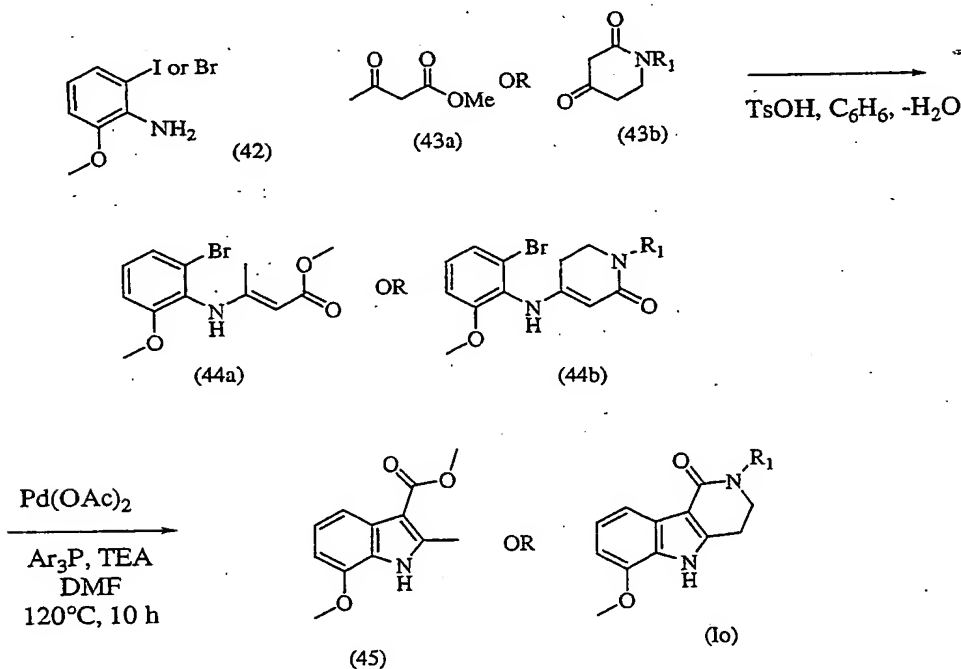
Compound (39) is treated with a nitrite such as NaNO_2 in aqueous acid (such as acetic acid) at elevated temperatures (preferably from about 50 to 140°C) to give compound of formula (II).

Compound of formula (II) is treated with R_3 -halide in the presence of a base such as sodium hydride to give a compound of formula (Im), wherein R_3 is other than hydrogen.

Compound of formula (Im) is hydrolyzed under aqueous basic conditions to form compound (41).

Compound (41) is coupled to an amine under standard amide bond coupling conditions (e.g. EDC/HOBT or acid chloride) to provide compounds of formula (In).

Scheme N



Scheme N shows a general procedure for Pd-catalyzed indole cyclizations that can be used to make compounds of formula (Io) or cannabinoid receptor modulators or intermediates (45) for making compounds of formula (I).

5 A mixture of ortho-halo aniline (42) and beta-keto ester (43a) or amide (43b) (1.2 equiv) are heated with azeotropic removal of water in the presence of an acid catalyst for 24 h to give enamides (44a) or (44b).

Pd-catalyzed cyclization of enamides (44a) or (44b) is carried out using 10-20 mole % Pd and 21-42 mole % phosphine ligand to give compounds (45) or
10 compounds of formula (Io). Tri-ortho tolyl phosphine is the preferred ligand. Isolation of the indoles can be performed by column chromatography.

Utility

Applicants have discovered that modulators to the cannabinoid receptor are effective for treating respiratory diseases. Respiratory diseases for which cannabinoid
15 receptor modulators are useful include but are not limited to chronic pulmonary obstructive disorder, emphysema, asthma, and bronchitis. Such cannabinoid receptor modulators include each of the compounds described in the examples herein, including compounds of formula (I), as well as those compounds described Examples 1-2, 14-16, and 67-71 herein. Applicants' discovery that cannabinoid receptor
20 modulators are useful for treating respiratory diseases also pertains to cannabinoid receptor modulators previously identified as effective for other uses, such as cannabinoid receptor modulators described in European Patent Documents Nos. EP 0570920 and EP 0444451; International Publications Nos. WO 97/29079, WO 99/02499, WO 98/41519, and WO 9412466; U.S. Patent Nos. 4,371,720, U.S.
25 5,081,122, U.S. 5,292,736, and U.S. 5,013,387; and French Patent No. FR 2735774.

Applicants also have discovered a group of novel cannabinoid receptor modulators of formula (I) useful for treating any cannabinoid-receptor mediated diseases, including the respiratory diseases referenced above and non-respiratory diseases. Exemplary non-respiratory cannabinoid receptor-mediated diseases include
30 transplant rejection, rheumatoid arthritis, multiple sclerosis, inflammatory bowel disease, lupus, graft v. host disease, T-cell mediated hypersensitivity disease,

psoriasis, Hashimoto's thyroiditis, Guillain-Barre syndrome, cancer, contact dermatitis, allergic rhinitis, and ischemic or reperfusion injury.

The compounds employed in the present invention for treatment of respiratory or non-respiratory diseases stimulate inhibitory pathways in cells, particularly in leukocytes, lung epithelial cells, or both, and are thus useful in treating such diseases. As used with reference to the utilities described herein, the term "treating" or "treatment" encompasses prevention, partial alleviation, or cure of the disease or disorder. "Leukocyte activation" is defined herein as any or all of cell proliferation, cytokine production, adhesion protein expression, and production of inflammatory mediators. "Epithelial cell activation" is defined herein as the production of any or all of mucins, cytokines, chemokines, and adhesion protein expression.

For example, CB2 receptor modulators are useful in treating a number of diseases mentioned above (for example, the treatment of inflammatory diseases), since CB2 receptor modulators prevent monocyte/macrophage activation and the release of inflammatory cytokines. The treatment of leukocyte-mediated diseases is one particularly preferred embodiment of the present invention through use of the compounds of formula (I). Compounds which selectively inhibit leukocyte activation and proliferation are preferred.

In addition, CB receptor modulators are useful in treating respiratory disorders. Such compounds block the activation of lung epithelial cells by moieties such as allergic agents, inflammatory cytokines or smoke, thereby limiting release of mucin, cytokines, and chemokines. Another preferred embodiment of the present invention comprises use of novel cannabinoid receptor modulator compounds to treat respiratory disease wherein the compounds selectively inhibit lung epithelial cell activation.

The cannabinoid receptor modulators for treating respiratory disease or non-respiratory diseases in accordance with the present invention may be used with other therapeutic agents such as those described below. Such other therapeutic agent(s) may be administered prior to, simultaneously with, or following the administration of the cannabinoid receptor modulators in accordance with the invention.

Exemplary of such other therapeutic agents which may be used in combination with cannabinoid receptor modulators include the following: cyclosporins (e.g., cyclosporin A), CTLA4-Ig, antibodies such as anti-ICAM-3, anti-IL-2 receptor (Anti-Tac), anti-CD45RB, anti-CD2, anti-CD3 (OKT-3), anti-CD4, anti-CD80, anti-CD86, monoclonal antibody OKT3, agents blocking the interaction between CD40 and gp39, such as antibodies specific for CD40 and/or gp39 (i.e., CD154), fusion proteins constructed from CD40 and gp39 (CD40Ig and CD8gp39), inhibitors, such as nuclear translocation inhibitors, of NF-kappa B function, such as deoxyspergualin (DSG), non-steroidal antiinflammatory drugs (NSAIDs) such as ibuprofen, steroids such as prednisone or dexamethasone, gold compounds, antiproliferative agents such as methotrexate, FK506 (tacrolimus, Prograf), mycophenolate mofetil, cytotoxic drugs such as azathioprine and cyclophosphamide, TNF- α inhibitors such as tenidap, anti-TNF antibodies or soluble TNF receptor such as etanercept (Enbrel), rapamycin (sirolimus or Rapamune), leflunomide (Arava), and cyclooxygenase-2 (COX-2) inhibitors such as celecoxib (Celebrex) and rofecoxib (Vioxx), or derivatives thereof, anticytokines such as antiIL-4 or IL-4 receptor fusion proteins and PDE 4 inhibitors such as Ariflo, and the PTK inhibitors disclosed in the following U.S. Patent Applications, incorporated herein by reference in their entirety: Serial No. 09/097,338, filed 6/15/98; Serial No. 09/094,797, filed 6/15/98; Serial No. 09/173,413, filed 10/15/98; and Serial No. 09/262,525, filed 3/4/99. See also the following documents and references cited therein and incorporated herein by reference: Hollenbaugh, D., *Et Al*, "Cleavable CD40Ig Fusion Proteins and the Binding to Sgp39", J. Immunol. Methods (Netherlands), 188(1), pp. 1-7 (Dec 15 1995); Hollenbaugh, D., *et al*, "The Human T Cell Antigen Gp39, A Member of the TNF Gene Family, Is a Ligand for the CD40 Receptor: Expression of a Soluble Form of Gp39 with B Cell Co-Stimulatory Activity", EMBO J (England), 11(12), pp. 4313-4321 (Dec 1992); and Moreland, L.W. *et al*, "Treatment of Rheumatoid Arthritis with a Recombinant Human Tumor Necrosis Factor Receptor (P75)-Fc Fusion Protein," New England J. of Medicine, 337(3), pp. 141-147 (1997).

The above other therapeutic agents, when employed in combination with the compounds of the present invention, may be used, for example, in those amounts

indicated in the Physicians' Desk Reference (PDR) or as otherwise determined by one of ordinary skill in the art.

Use of the compounds of the present invention as encompassed by formula (I) in treating leukocyte activation-associated disorders is exemplified by, but is not limited to, treating a range of disorders such as: transplant (such as organ transplant, acute transplant, xenotransplant or heterograft or homograft (such as is employed in burn treatment)) rejection; protection from ischemic or reperfusion injury such as ischemic or reperfusion injury incurred during organ transplantation, myocardial infarction, stroke or other causes; transplantation tolerance induction; arthritis (such as rheumatoid arthritis, psoriatic arthritis or osteoarthritis); multiple sclerosis; respiratory and pulmonary diseases including but not limited to chronic obstructive pulmonary disease (COPD), emphysema, bronchitis, and acute respiratory distress syndrome (ARDS); inflammatory bowel disease, including ulcerative colitis and Crohn's disease; lupus (systemic lupus erythematosus); graft vs. host disease; T-cell mediated hypersensitivity diseases, including contact hypersensitivity, delayed-type hypersensitivity, and gluten-sensitive enteropathy (Celiac disease); psoriasis; contact dermatitis (including that due to poison ivy); Hashimoto's thyroiditis; Sjogren's syndrome; Autoimmune Hyperthyroidism, such as Graves' Disease; Addison's disease (autoimmune disease of the adrenal glands); Autoimmune polyglandular disease (also known as autoimmune polyglandular syndrome); autoimmune alopecia; pernicious anemia; vitiligo; autoimmune hypopituitarism; Guillain-Barre syndrome; other autoimmune diseases; glomerulonephritis; serum sickness; urticaria; allergic diseases such as respiratory allergies (asthma, hayfever, allergic rhinitis) or skin allergies; scleroderma; mycosis fungoides; acute inflammatory and respiratory responses (such as acute respiratory distress syndrome and ischemia/reperfusion injury); dermatomyositis; alopecia areata; chronic actinic dermatitis; eczema; Behcet's disease; Pustulosis palmoplanteris; Pyoderma gangrenum; Sezary's syndrome; atopic dermatitis; systemic sclerosis; and morphea. The term "leukocyte activation-associated" or "leukocyte-activation mediated" disease as used herein includes each of the above referenced diseases or disorders. In a particular embodiment, the compounds of the present invention are useful for treating the aforementioned exemplary disorders irrespective of their etiology. The combined

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activity of the present compounds towards monocytes, macrophages, T-cells, etc. may be useful in treating any of the above-mentioned disorders.

Cannabinoid receptors are important in the regulation of Fc gamma receptor responses of monocytes and macrophages. Compounds of the present invention inhibit the Fc gamma dependent production of TNF alpha in human monocytes/macrophages. The ability to inhibit Fc gamma receptor dependent monocyte and macrophage responses results in additional anti-inflammatory activity for the present compounds. This activity is especially of value, for example, in treating inflammatory diseases such as arthritis or inflammatory bowel disease. In particular, the present compounds are useful for treating autoimmune glomerulonephritis and other instances of glomerulonephritis induced by deposition of immune complexes in the kidney that trigger Fc gamma receptor responses leading to kidney damage.

Cannabinoid receptors are expressed on lung epithelial cells. These cells are responsible for the secretion of mucins and inflammatory cytokines/chemokines in the lung and are thus intricately involved in the generation and progression of respiratory diseases. Cannabinoid receptor modulators regulate both the spontaneous and the stimulated production of both mucins and cytokines. Thus, such compounds are useful in treating respiratory and pulmonary diseases including, COPD, ARDS, and bronchitis.

Cannabinoid receptors may be expressed on gut epithelial cells and hence regulate cytokine and mucin production and may be of clinical use in treating inflammatory diseases related to the gut. Cannabinoid receptors are also expressed on lymphocytes, a subset of leukocytes. Thus, cannabinoid receptor modulators will inhibit B and T-cell activation, proliferation and differentiation. Thus, such compounds will be useful in treating autoimmune diseases that involve either antibody or cell mediated responses such as multiple sclerosis and lupus.

In addition, cannabinoid receptors regulate the Fc epsilon receptor and chemokine induced degranulation of mast cells and basophils. These play important roles in asthma, allergic rhinitis, and other allergic disease. Fc epsilon receptors are stimulated by IgE-antigen complexes. Compounds of the present invention inhibit the

Fc epsilon induced degranulation responses, including the basophil cell line, RBL. The ability to inhibit Fc epsilon receptor dependent mast cell and basophil responses results in additional anti-inflammatory and anti-allergic activity for the present compounds. In particular, the present compounds are useful for treating asthma, allergic rhinitis, and other instances of allergic disease.

Membrane Binding Assay Using Human CB1 or CB2

The following assay has been carried out using the human cannabinoid receptor expressed in CHO cells.

Radioactive tracer label (WIN 55,212-2 Mesylate [5,7-3H] for CB2, CP55,940 for CB1) and test compound are incubated together in a 96-well tissue culture plate. All reagents are dissolved or resuspended in binding buffer (10mM HEPES, pH 7.4, 1mM EDTA, 5mM MgCl₂, 0.3% BSA). The reaction is initiated by the addition of membranes (50 ug) from CHO-K1 cells expressing either CB1 or CB2). The plates are incubated 2 hours with shaking at room temperature and the reaction is harvested on a Wallac Filtermat B with 7 wash cycles using wash buffer (10mM HEPES, pH 7.4, 0.1% BSA). The filter is counted in a Betaplate scintillation counter to ascertain the cannabinoid inhibitory activity of the test compound (activity inversely proportional to the amount of labeled WIN-55212-2 incorporated). Routinely the radiolabel was used at a concentration of 10 nM but the exact concentration of reagents and the amount of label can be varied as needed.

This assay is advantageous as it can be conducted in a 96-well format that is readily automated. Different labeled cannabinoid ligands can be substituted into the assay. The recombinant cannabinoid receptors may be obtained from commercial sources and can be expressed in CHO or insect cell culture (*Spodoptera frugiperda* cells).

Cell assays

(1) Monocyte/Macrophage cytokine production

Freshly isolated human monocytes, or the human monocytic cell line THP-1, are incubated at 1×10^6 cells /ml in RPMI 1640 media containing 10%FBS with the test compound for 30 minutes and then stimulated by the addition of either

lipopolysaccharide (LPS) or immune complexes (IC). Cells are incubated for 6 h at 37°C at which time the cell supernatants are removed and assayed for cytokines (TNF, IL-1 β , IL-6, IL-8) using commercially available ELISA kits. The cannabinoid agonists inhibit the production of inflammatory cytokines.

5

(2) Activation of Lung Epithelial Cells

The ability of the cannabinoids to inhibit mucin, chemokine/cytokine production from lung epithelial cells is evaluated with human lung epithelial cell lines H292 and A549. Epithelial cells are cultured overnight in 48 well microtiter plates in complete RMPI 1650 (200 μ l/well) at a density of 2×10^5 cells/ml. The media is removed and replaced with fresh media. Test compounds in 50 μ l isotonic buffer are added and incubated for 1 hour at 37°C. Cell activation is triggered by the addition of a stimulatory agent comprising one of EGF, smoke conditioned media, TNF- α or IL-1 β . In this assay, the IC₅₀ for Win-55212-2 <20 mM. After a desired period of time (e.g., 24h) the cell supernatants are removed and assayed for mucin cytokine and chemokines by ELISA. The cannabinoid agonists inhibit mucin and IL-8 production from lung epithelial cells.

In addition to Win-55212-2 (described in French Patent document FR 2,735,774 A1, incorporated herein), compounds of formula (I) demonstrated activity in the above lung epithelial cell assay, particularly indole and indazole-based amino acid esters described herein.

(3) T cell Proliferation Assays

The ability of the cannabinoids to inhibit the proliferation of normal human peripheral blood T cells that have been stimulated to grow with anti-CD3 plus anti-CD28 antibodies is evaluated. A 96 well plate is coated with a monoclonal antibody to CD3 (such as G19-4), the antibody is allowed to bind, and then the plate is washed. The antibody bound to the plate serves to stimulate the cells. Normal human peripheral blood T cells are added to the wells along with test compound plus anti-CD28 antibody to provide co-stimulation. After a desired period of time (e.g., 3 days), the [3H]-thymidine is added to the cells, and after further incubation to allow

incorporation of the label into newly synthesized DNA, the cells are harvested and counted in a scintillation counter to measure cell proliferation.

(4) Degranulation of RBL-cells

RBL 2H3 cells are cultured overnight in complete MEM at a density of 1×10^6 cells/ml at 37°C in 100 µl medium. Test compounds in 50 µl isotonic buffer are added and incubated for 2 hours at 37°C. Cell degranulation is triggered by the addition of 25 µl DNP-BSA IgE complex (300 ng/ml DNP-BSA) and incubated an additional 30 min. at 37°C. Fifty µl of the cell supernatant from each well is removed and placed in a second 96-well plate which contains 50 µl of substrate solution [90 ml NAGA (hex) buffer (70 ml 0.2M NaPO₄, 20 ml 0.4M Citric Acid Monohydrate pH 4.5) + 135 ml dH₂O, 615 mg p-Nitrophenyl N-acetyl D-glucosaminide]. The reaction is stopped by the addition of 100 µl NAGA stop solution (0.2M Glycine, 0.2M NaCl, 0.2M NaOH) and the plate read at 405nm on a microtiter plate reader. The compounds of the Examples herein show a desired activity in the assays described.

Examples

The following Examples illustrate embodiments of the present invention and are not intended to limit the scope of the claims.

20 Abbreviations

The following abbreviations are employed hereinbefore and in the Examples:

Ph = phenyl
Bn = benzyl
t-Bu = tertiary butyl
25 Me = methyl
Et = ethyl
MeOH = methanol
EtOH = ethanol
Et₂O = diethyl ether
30 EtOAc = ethyl acetate
Pen = pentyl
Boc = tert-butyloxycarbonyl
BOP chloride = bis-(2-oxo-3-oxazolidinyl)phosphinic chloride
Cbz = carbobenzyloxy or carbobenzoxy or benzyloxycarbonyl
35 Cbz-Cl = benzyl chloroformate
m-CPBA = meta chloroperbenzoic acid

- hex = hexane(s)
Morph = morpholine or morpholinyl
BOP reagent = benzotriazol-1-yloxy-tris (dimethylamino) phosphonium
hexafluorophosphate
- 5 EDC or EDCI = 3-ethyl-3'-(dimethylamino)propyl- carbodiimide
EDC.HCl = EDC hydrochloride
DBU = 1,8-diazabicyclo[5.4.0]undec-7-ene
DCC = dicyclohexylcarbodiimide
DCE = 1,2 dichloroethane
- 10 DCM= dichloromethane
DEAD = diethyl azodicarboxylate
DIAD = diisopropyl azodicarboxylate
DIPEA = diisopropylethylamine
DMA.HCl = dimethylamine hydrochloride
- 15 DMAP = 4-dimethylaminopyridine
DME = 1,2 dimethoxyethane
DMF = dimethyl formamide
DMSO = dimethyl sulfoxide
DIBALH = diisobutyl aluminum hydride
- 20 HATU = [O-(7-azabenzotriazol-1-yl)-1,1,3,3-tetramethyluronium]
hexafluorophosphate
HOAc or AcOH = acetic acid
HOBT or HOBT.H₂O = 1-hydroxybenzotriazole hydrate
HOAT = 1-Hydroxy-7-azabenzotriazole
- 25 LDA = lithium diisopropylamide
NBS = N-bromosuccinimide
NCS = N-chlorosuccinimide
NMM = N-methyl morpholine
TFA = trifluoroacetic acid
- 30 TEA = triethylamine
THF = tetrahydrofuran
Cs₂CO₃ = cesium carbonate
HCl = hydrochloric acid or hydrochloride
KOH = potassium hydroxide
- 35 K₂CO₃ = potassium carbonate
LiAlH₄ = lithium aluminum hydride
LiOH = lithium hydroxide
n-BuLi = n-butyllithium
t-BuLi = t-butyllithium
- 40 NaCl = sodium chloride
NaOH = sodium hydroxide
NaHCO₃ = sodium bicarbonate
Pd/C = palladium on carbon
Ph₃P = triphenylphosphine
- 45 Pd(OAc)₂ = Palladium acetate
Pd(Ph₃P)₄ = tetrakis triphenylphosphine palladium
Ar = argon
N₂ = nitrogen

- DI = deionized
min = minute(s)
h or hr = hour(s)
L = liter
5 mL = milliliter
μL = microliter
g = gram(s)
mg = milligram(s)
mol = moles
10 mmol = millimole(s)
meq = milliequivalent
RT = room temperature
ret. t. = HPLC retention time (minutes)
sat or sat'd = saturated
15 aq. = aqueous
TLC = thin layer chromatography
HPLC = high performance liquid chromatography
LC/MS = high performance liquid chromatography/mass spectrometry
MS or Mass Spec = mass spectrometry
20 NMR = nuclear magnetic resonance
mp = melting point

HPLC Conditions

- When a letter is given in a parenthetical following the HPLC retention times,
25 this reference denotes the HPCL conditions. HPLC retention times were determined
using a linear elution gradient of mixtures of solvent A and solvent B (solvent A =
10% MeOH/90% water/0.1% TFA and solvent B = 90% MeOH/10% water/0.1%
TFA) where the gradient begins with 100% solvent A and increases in a linear rate to
100% solvent B over the specified total elution time. All products were detected
30 using a UV detector at a wavelength of 220 nm.

Condition A: YMC S5 ODS 4.6 mm x 50 mm Ballistic chromatography
column with a 4 minute total gradient elution time and a flow rate of 4 mL/minute.

Condition B: YMC S5 Pro 4.6 mm x 33 mm Ballistic chromatography
column with a 2 minute total gradient elution time and a flow rate of 5 mL/minute.

- 35 Condition C: YMC S5 Turbopak Pro 4.6 mm x 33 mm Ballistic
chromatography column with a 2 minute total gradient elution time and a flow rate of
5 mL/minute.

Condition D: YMC ODSA 5u C18 4.6 mm x 50 mm Ballistic chromatography column with a 4 minute total gradient elution time and a flow rate of 4 mL/minute.

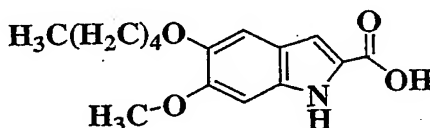
Condition E: YMC S5 Turbopak Pro 4.6 mm x 33 mm Ballistic chromatography column with a 2 minute total gradient elution time and a flow rate of 4 mL/minute.

Tables

In the tables, structures are provided for the compounds of the examples. In some instances a nitrogen atom may be shown bonded to two groups; since nitrogen has a valency of three, it should be understood in those instances that the nitrogen group is also bonded to a hydrogen atom. A bond extending from a ring or chain may denote a methyl group, as reflected by the compound names.

Example 1

5-pentyloxy-6-methoxyindole-2-carboxylic acid



A. N-phenylsulfonyl 5-benzyloxy-6-methoxyindole

A solution of 5-benzyloxy-6-methoxyindole (990 mg, 3.9 mmol) in DMF (3 mL) was added to a solution of NaH (234 mg, 5.9 mmol, 60% in oil) in DMF (1 mL) at 0°C. The ice bath was removed, and the reaction mixture allowed to stir at RT for 30 min. The reaction flask was cooled to 0°C and PhSO₂Cl (0.6 mL, 4.7 mmol) was added via syringe. The ice bath was removed and the reaction mixture stirred at RT for 24 h. Water (25 mL) was added and the aqueous layer extracted with Et₂O (4x50 mL). The combined organic extracts were washed with brine, dried over Na₂SO₄, filtered and concentrated *in vacuo* to give an oil. The residue was purified by column chromatography (25% then 40% EtOAc/hex) to furnish N-phenylsulfonyl 5-benzyloxy-6-methoxyindole as a crystalline solid (1.38 g, 90% yield).

B. Ethyl N-phenylsulfonyl 5-benzyloxy-6-methoxyindole-2-carboxylate

To a solution of compound A (120 mg, 0.3 mmol) in THF at -78°C was added nBuLi dropwise (140 μL , 0.35 mmol, 2.57M in hex), and the reaction mixture was stirred at 0°C for 20 min. The reaction mixture was recooled to -78°C , ClCO_2Et (37 μL , 0.38 mmol) was added, and the mixture was stirred for 45 min and then
5 allowed to warm to RT slowly. The reaction mixture was quenched with sat aq. NH_4Cl , diluted with water, and extracted into EtOAc (3x40 mL). The combined organic extracts were dried over Na_2SO_4 , filtered, and concentrated *in vacuo* to give an oil. The residue was purified by column chromatography (25% EtOAc/hex) to furnish the above-titled compound B as a yellow glass which was used directly in the
10 next step.

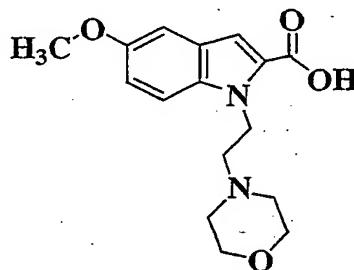
C. Ethyl *N*-phenylsulfonyl 5-hydroxy-6-methoxyindole-2-carboxylate
Hydrogenolysis of Compound B in 1/1 MeOH/EtOAc with 10% Pd-C/ H_2 balloon followed by column chromatography (50% EtOAc/hex) furnished the above-
15 titled compound C (77 mg, 58% yield).

D. Ethyl *N*-phenylsulfonyl 5-pentyloxy-6-methoxyindole-2-carboxylate
To a solution of compound C (38 mg, 0.17 mmol), K_2CO_3 (36 mg, 0.27 mmol) in DMF (2 mL) was added 1-bromopentane (27 μL , 0.21 mmol), and the reaction was
20 heated at 65°C for 18h. Another 30 μL of 1-bromopentane was added, and the reaction was heated to 85°C for another 18h. The reaction was cooled, poured into water (10 mL) and extracted with Et_2O (3x50 mL). The combined organic extracts were dried over MgSO_4 , filtered, and concentrated *in vacuo* to give an oil. The residue was purified by column chromatography (10% EtOAc/hex) to furnish the
25 above-titled compound D as a white crystalline solid (36 mg, 73% yield).

E. 5-Pentyloxy-6-methoxyindole-2-carboxylate
Treatment of ethyl *N*-phenylsulfonyl 5-pentyloxy-6-methoxyindole-2-carboxylate (Compound D) with 3 N NaOH (0.3 mL) in EtOH (2 mL) at reflux for 24
30 h followed by the usual workup (as outlined above) afforded 5-pentyloxy-6-methoxyindole-2-carboxylic acid.

Example 2

1-[2-(Morpholino)ethyl]-5-methoxy-2-indolecarboxylate



5 A. 1-[2-(Morpholino)ethyl]-5-methoxy-2-indolecarboxylate methyl ester

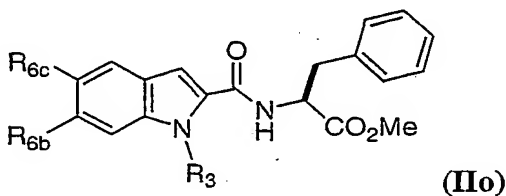
A solution of methyl 5-methoxy-2-indolecarboxylate (36 mg, 0.17 mmol) and N-(2-chloroethyl)morpholine.HCl (39 mg, 0.21 mmol) in DMF (2 mL) at 0°C was added to NaH (18 mg, 0.44 mmol, 60% in oil) in one portion. The ice bath was removed and the reaction mixture allowed to stir for 1 h at RT and then at 65°C for 16 h. Water (2 mL) was added and the mixture was partitioned between EtOAc and water. Upon extraction with EtOAc (3x25 mL), the combined organic extracts were dried over Na₂SO₄, filtered, and concentrated *in vacuo*. The residue was purified by column chromatography (25% then 50% EtOAc/hex) to furnish the above-titled compound A as a white solid (32 mg, 58% yield).

15

B. 1-[2-(Morpholino)ethyl]-5-methoxy-2-indolecarboxylate

The methyl ester from step A (31.2 mg, 0.4 mmol) was stirred in a mixture of 3N NaOH (0.5 mL) and EtOH (3 mL) for 20 h, acidified with conc. HCl/ pH 7.0 buffer, and extracted into EtOAc. The combined extracts were dried over Na₂SO₄, filtered, and concentrated *in vacuo* to yield the compound of Example 2.

20

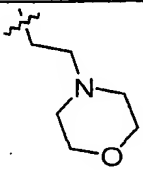
Examples 3-12

The following procedure was used to prepare the compounds of Examples 3-12 having formula (IIo), wherein the values for R_{6b} , R_{6c} and R_3 are as shown in Table 1 below.

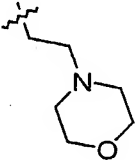
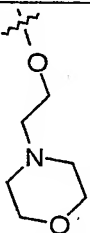
General Procedure

- 5 To a solution of carboxylic acid (0.54 mmol), L-phenylalanine methyl ester (118 mg, 0.54 mmol), EDC (120 mg, 0.6 mmol), HOBT (82 mg, 0.6 mmol) in DCM (5 mL) was added DIPEA (280 μ L, 1.6 mmol), and the reaction mixture was stirred at RT for 7h. The reaction mixture was poured into DCM (50 mL) and washed with water (15mL). The organic layer was dried over Na_2SO_4 , filtered, and concentrated *in vacuo*. The residue was purified by column chromatography (25% then 40% then 50% EtOAc/hex) to furnish the appropriate amide.

TABLE 1

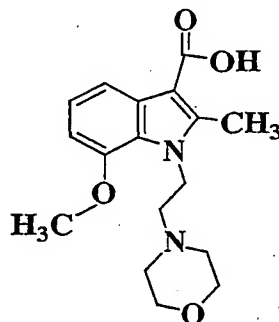
EX. NO	R_{6b}	R_{6c}	R_3	COMPOUND NAME	DATA MS (M+H) and HPLC ret. t (min). and conditions
3	OMe	OPen	H	N-[[6-Methoxy-5-(pentyloxy)-1H-indol-2-yl]carbonyl]-L-phenylalanine methyl ester	438.2/4.36 (A)
4	H	OMe	H	N-[(5-Methoxy-1H-indol-2-yl)carbonyl]-L-phenylalanine methyl ester	352.2/3.02 (A)
5	OBn	OMe	H	N-[[5-Methoxy-6-(phenylmethoxy)-1H-indol-2-yl]carbonyl]-L-phenylalanine methyl ester	459.3/3.39 (A)
6	H	OPen	H	N-[[5-(Pentyloxy)-1H-indol-2-yl]carbonyl]-L-phenylalanine methyl ester	409.3/4.47 (A)
7	OPen	OMe	H	N-[[5-Methoxy-6-(pentyloxy)-1H-indol-2-yl]carbonyl]-L-phenylalanine methyl ester	439.3/4.24 (A)
8	H	OMe		N-[[5-Methoxy-1-[2-(4-morpholinyl)ethyl]-1H-indol-2-yl]carbonyl]-L-phenylalanine methyl ester	465.3/2.98 (A)
9	OMe	H	H	N-[(6-Methoxy-1H-indol-2-yl)carbonyl]-L-phenylalanine methyl ester	352.5/3.70 (A)

10	OMe	H	CH ₃	N-[(6-Methoxy-1-methyl-1H-indol-2-yl)carbonyl]-L-phenylalanine methyl ester	366.2/3.87 (A)
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11	OMe	H		N-[[6-Methoxy-1-[2-(4-morpholinyl)ethyl]-1H-indol-2-yl]carbonyl]-L-phenylalanine methyl ester	465.2/3.06 (A)
12	H		H	N-[[5-[2-(4-Morpholinyl)ethoxy]-1H-indol-2-yl]carbonyl]-L-phenylalanine methyl ester	451.2/2.73 (A)

Example 13a

1-(4-Ethylmorpholinyl)-2-methyl-7-methoxyindole-3-carboxylic acid



5

A. 1-(2-Nitro-3-methoxyphenyl)-2-nitropropanol

To a 2L round-bottomed flask equipped with a magnetic stirrer and a N₂ bubbler were added 2-nitro-3-methoxybenzaldehyde (125.7 g, 0.6939 mol), nitroethane (73 g, 0.97 mol), 18-C-6 (18 g), isopropanol (420 mL) and KF (20 g).

10 The mixture was stirred at RT for 16h. The solvent was removed under vacuum to give an oil. Isopropanol (100 mL) and water (250 mL) were added. The mixture was placed under vacuum to give a slurry. The slurry was stirred for 1h and filtered. The

cake was washed with water (4x100 mL) and dried to give 1-(2-nitro-3-methoxyphenyl)-2-nitropropanol as a diastereomeric mixture in a ratio of 3:2 (170.3 g, 96% yield). ¹H NMR for major isomer (CDCl₃) δ 1.38 (d, J=6.9Hz, 3H), 2.94 (s, 1H), 3.92 (s, 3H), 4.90 (m, 1H), 5.08 (d, J=8.6Hz, 1H), 7.05-7.52 (m, 3H). ¹H NMR for minor isomer (CDCl₃) δ 1.55 (d, J=6.9Hz, 3H), 2.94 (s, 1H), 4.80 (m, 1H), 5.46 (d, J=3.0Hz), 7.05-7.52 (m, 3H).

B. 1-(2-Nitro-3-methoxyphenyl)-2-nitropropene

To a 5L three-necked round-bottomed flask equipped with a mechanical stirrer and a N₂ bubbler were added 1-(2-nitro-3-methoxyphenyl)-2-nitropropanol (170 g, 0.66 mol), acetic anhydride (450 mL), 18-Crown-6 (17 g) and KF (38.25 g). The reaction mixture was stirred at RT for 64h, then cooled in an ice-water bath. Water (2250 mL) was added slowly. The resulting slurry was stirred at 0°C for 2h and then filtered. The cake was washed with DI water (3x250 mL) and suction dried for 20h to give 1-(2-nitro-3-methoxyphenyl)-2-nitropropene (150.7 g, 96% yield). ¹H NMR (CDCl₃) δ 2.30 (s, 3H), 3.95 (s, 3H), 6.94 (d, J=7.8Hz, 1H), 7.13 (d, J=8.5Hz, 1H), 7.53 (pseudo t, J=8.1Hz, 1H), 7.89 (s, 1H).

C. 2-Methyl-7-methoxyindole

To a 2L hydrogenation flask were added 1-(2-Nitro-3-methoxyphenyl)-2-nitropropene (44 g, 0.1850 mol), 10% Pd/C (4.4g, ~50% water wet), EtOAc (600 mL), acetic acid (90 mL) and absolute EtOH (75 mL). The reaction mixture was hydrogenated at <60 psi for 3h and then filtered. The cake was washed with EtOAc (3x100 mL). The filtrate was concentrated to remove EtOAc and EtOH. DI water (200 mL) was then added slowly. The resulting slurry was stirred for 0.5h at RT and filtered. The cake was washed with 1:2 HOAc/H₂O (2x30 mL) 1:4 HOAc/H₂O (50 mL), water (2x80 mL) and suction dried for 18h to give 2-methyl-7-methoxyindole (8.3 g, 62% yield). ¹H NMR (CDCl₃) δ 2.42 (s, 3H), 3.94 (s, 3H), 6.18 (pseudo t, J=1.1Hz, 1H), 6.57 (d, J=7.7Hz, 1H), 6.97 (pseudo t, J=7.7Hz, 1H), 7.12 (d, J=7.7Hz, 1H), 8.10 (s, 1H).

D. 1-[2-(4-Morpholino)ethyl]-2-methyl-3-methoxymethyl-7-methoxyindole

To a stirred suspension of N-(2-chloroethyl)morpholine hydrochloride (13 g, 0.07 mol) was added (13.2 g, 0.2 mol) in 100 mL of DMSO of 85% powdered KOH. After stirring for 10 minutes, the reaction mixture was heated to 100°C and then stirred at this temperature for 3-5 h. The reaction mixture was cooled to RT and
5 diluted with 100 mL of water and 200 mL of ether. The organic layer was separated, and the aqueous layer was extracted with ether (2x100 mL). The organic layers were combined, washed with water (2x100 mL) and dried over anhydrous Na₂SO₄ and filtered. The solvent was removed under reduced pressure to give the above compound D as a light yellow oil (13.59 g, 99% yield). ¹H NMR (CDCl₃) δ 2.42 (s,
10 3H), 2.52 (m, 4H), 2.62 (t, J=7.1Hz, 2H), 3.75 (m, 4H), 3.90 (s, 3H), 4.42 (t, J=7.1Hz, 2H), 6.17 (s, 1H), 6.55 (d, J=7.8 Hz, 1H), 6.90 (dd, J=7.8, 8.0Hz, 1H), 7.10 (d, J=8.0Hz, 1H).

15 E. 1-[2-(4-Morpholino)ethyl]-2-methyl-3-trichloroacetyl-7-methoxyindole hydrochloride

To a solution of the methoxyindole from step D (13 g, 0.048 mol) in DCE (400 mL) was added trichloroacetyl chloride (26 g, 0.14 mol). The solution was refluxed for 6-8 h and then cooled to RT. The resulting slurry was filtered, washed
20 with ether (2x100 mL) and dried to give the above-titled methoxyindole hydrochloride (21 g, 94% yield). ¹H NMR (CDCl₃) δ 2.85 (s, 3H), 2.95 (m, 2H), 3.30 (m, 2H), 3.55(m, 2H), 4.05 (m, 5H), 4.32 (m, 2H), 5.15 (m, 2H), 6.75 (d, J=7.8Hz, 1H), 7.15 (dd, J=7.8, 8.0Hz, 1H), 7.85 (d, J=8.0Hz, 1H).

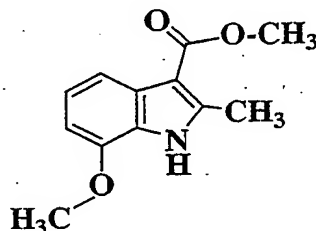
25 F. 1-[(4-Morpholino)ethyl]-2-methyl-7-methoxyindole-3-carboxylic acid

To a solution of the compound from step E (19 g, 0.048 mol) in THF (100 mL) was added NaOH solution (100 mL, 1N, 0.1 mol). The reaction mixture was stirred about 1-2 h. The resulting slurry was filtered and washed with ether (2x50mL). The filtrate was transferred into a separation funnel and the phases were
30 separated. The aqueous layer was washed with ether (2x100 mL). The cake and aqueous layer were combined and the pH adjusted to 4 with HCl (6N). The slurry was filtered, washed with ether (2x100 mL), and the solid was dried to give the above-titled carboxylic acid (15 g, 95% yield). ¹H NMR (DMSO-d₆) δ 2.44 (s, 3H),

2.58 (s, 2H), 2.72(s, 4H), 3.56 (s, 4H), 3.90(s, 3H), 4.42 (s, 2H), 6.67 (d, J=7.8Hz, 1H), 7.00 (dd, J=7.8, 8.0Hz, 1H), 7.65 (d, J=8.0Hz, 1H).

Example 13b

2-Methyl-3-methoxycarbonyl-7-methoxyindole



5

A. 2-Methyl-3-trichloroacetyl-7-methoxyindole

To a 2L round-bottomed flask equipped with a magnetic stirrer and a N₂ bubbler were added 2-methyl-7-methoxyindole (12 g, 74 mmol), acetonitrile (125 mL) and collidine (15 mL, 113 mmol). The mixture was stirred to give a solution and was cooled with an ice water bath. Trichloroacetyl chloride (14 mL, 112 mmol) was added. The cooling bath was removed and the reaction mixture stirred at RT for 3h. 1N HCl (500 mL) was then added over 10 minutes. The resulting slurry was stirred at RT for 30 minutes and filtered. The cake was washed with DI water (3x50 mL) and suction dried for 17h to give 2-methyl-3-trichloroacetyl-7-methoxyindole (22.8 g, 96% yield). ¹H NMR (CDCl₃) δ 2.79 (s, 3H), 3.96 (s, 3H), 6.71 (d, J=7.9Hz, 1H), 7.19 (dd, J=7.9, 8.4Hz, 1H), 7.82 (d, J=8.4Hz, 1H), 8.92 (s, 1H).

15

B. 2-Methyl-3-methoxycarbonyl-7-methoxyindole

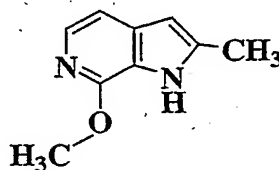
To a 1L round-bottomed flask equipped with a magnetic stirrer and a N₂ bubbler were added 2-methyl-3-trichloroacetyl-7-methoxyindole (22.8 g, 74.37 mmol) and MeOH (150 mL). The mixture was stirred at RT to give a slurry. KOH (42.5 wt%, 2 mL) was added and the reaction stirred for 5 min. HCl (0.1N, 500 mL) was added dropwise. The slurry was stirred at RT for 1h and filtered. The cake was washed with DI water (3x30 mL) and suction dried for 18h to give 2-methyl-3-methoxycarbonyl-7-methoxyindole (15.57 g, 96% yield). ¹H NMR (CDCl₃) δ 2.71 (s, 3H), 3.89 (s, 3H), 3.92 (s, 3H), 6.63 (d, J=7.9Hz, 1H), 7.12 (dd, J=7.9, 8.0Hz, 1H), 7.66 (d, J=8.0Hz, 1H), 8.84 (s, 1H).

20

25

Example 14

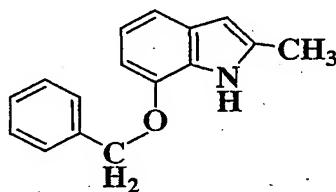
2-Methyl-7-methoxy-6-azaindole



5 2-Methoxy-3-nitro-4-methyl pyridine (200 mg, 1.2 mmol) and dimethylacetamide dimethylacetal (0.5 mL) were heated at 130°C for 18 h. The reaction mixture was cooled and concentrated *in vacuo* to a deep purple-red oil. Benzene (4 mL) and 10% Pd/C (25 mg) were added and the solution hydrogenated at 45 psi for 18h (Parr apparatus). The red coloration disappeared. The crude reaction
10 mixture was purified directly by silica gel chromatography (20% EtOAc/hex) to furnish 2-methyl-7-methoxy-6-azaindole (112 mg, 57 % yield). LC-MS 163.1, M+H.

Example 15

2-Methyl-7-benzyloxy indole



15

A. 2-Methyl-7-hydroxy indole

To a solution of 2-methyl-7-methoxy indole (814 mg, 5.0 mmol) in CH₂Cl₂ (20 mL) at 0°C was added BBr₃ (15 mL, 15 mmol, 1M in CH₂Cl₂), and then the ice
20 bath was removed and stirring was continued for 3 h. Ice was added and the reaction mixture diluted with water (30 mL). The aqueous layer was extracted with EtOAc (3x100 mL), dried over Na₂SO₄, filtered, and concentrated *in vacuo*. The residue was purified via passage through a short silica gel column (20% then 50% EtOAc/hex) to afford 2-methyl-7-hydroxy indole as an unstable solid (99% yield).

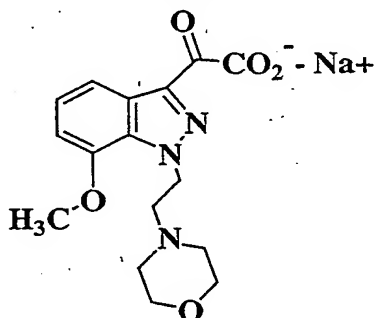
25

B. 2-Methyl-7-benzyloxy indole

To the compound from step A, acetone (15 mL) was added followed by benzyl bromide (670 μ L, 5.6 mmol) and Cs_2CO_3 (1.8 g, 5.6 mmol) and the reaction mixture stirred at RT for 18 h. A second aliquot of BnBr (140 μ L) and Cs_2CO_3 (380 mg) was added and stirring continued for 24 h. The reaction mixture was poured into EtOAc and water, the layers were separated, and the aqueous layer was further extracted with EtOAc (3x50 mL). The combined organic extracts were washed with 1N NaOH and water and dried over MgSO_4 , filtered, and concentrated *in vacuo*. Purification by column chromatography (hexanes then 5% EtOAc/hex) afforded 2-methyl-7-benzyloxy indole as an unstable solid (898 mg, 81% yield). ^1H NMR impure; 238.17, M+H.

Example 16

7-Methoxy-1-morpholinoethyl indazole-3-carboxylic acid, sodium salt



A. 3-Methoxy-2-(tert-butyloxy)amino]phenylacetic acid dimethyl acetamide

To a solution of 3-methoxy-2-[(tert-butyloxy)amino]-phenylacetic acid (8.3 g, 30 mmol) and EDC.HCl (8.51 g, 44.4 mmol) were added 1-hydroxybenzotriazole (4.80 g, 35.5 mmol) and DMA.HCl (9.7 g, 120 mmol) in 90 mL of DMF at RT. DIPEA (26 mL, 148 mmol) was added, and the resulting solution was stirred for 48 h. The reaction mixture was concentrated *in vacuo* and the resulting oil was dissolved in 350 mL of DCM and washed with aqueous 1 N NaOH (3 x 125 mL), 6% aqueous citric acid solution (3 x 100 mL), water (100 mL), and brine (100 mL). After drying over anhydrous sodium sulfate, the resulting solution was decanted and concentrated on a rotary evaporator to afford a reddish-orange oil as the crude product. This material was dissolved in Et_2O (ca 100 mL) and reconcentrated on the rotary

evaporator yielding a yellow solid that was subsequently triturated with two 35-mL portions of hexanes to remove any residual DMF. The resulting solid was dried *in vacuo* to give the above-titled compound A (7.1 g, 78% yield) as a yellow solid. LC-MS (MH^+ 309.2).

5

B. 7-Methoxy-3-dimethylamido indazole

To a stirring solution of 1.3 g (4.12 mmol) of compound A in 4% aqueous acetic acid at 95°C was slowly added an aqueous solution of 0.85 g (12.4 mmol) of sodium nitrite in 1.4 mL of water over 2 h. After the addition was complete, HPLC
10 analysis showed nearly complete consumption of the substrate. The reaction mixture was cooled to RT and concentrated on a rotary evaporator, and the resulting solid was suspended in approximately 30 mL of water. The product was collected by vacuum filtration and washed with water (20 mL), then dried *in vacuo* to afford the above-titled compound B (0.74 g, 82%) as a yellow solid.

15

C. 7-Methoxy-1-morpholinoethyl-3-dimethylamido indazole

To a RT solution of 0.55 g (2.50 mmol) of compound B and 0.75 g (5.00 mmol) of 4-(2-chloroethyl)morpholine in 5 mL of anhydrous DMF was added 0.2 g (5.00 mmol) of 60% sodium hydride dispersion in two portions over 10 minutes. The
20 reaction mixture was allowed to stir at RT for 14 h, then an additional 0.75 g (5.00 mmol) of 4-(2-chloroethyl)morpholine was added, and the mixture was heated to 40°C for an additional 2 h. The mixture was allowed to cool to RT and slowly 10 mL of water was added. The mixture was extracted with EtOAc (4 x 30 mL), and the combined extracts were washed with water (3 x 7 mL), brine (7 mL), then dried over
25 anhydrous sodium sulfate, decanted, and concentrated *in vacuo* to afford a yellow liquid which partially solidified upon standing. This material was triturated with three 20-mL portions of hexanes and the remaining white solid was dried *in vacuo* to afford 0.60 g (72%) of the above-titled compound C. LC-MS (MH^+ 333.3).

30

D. 7-Methoxy-1-morpholinoethyl indazole-3-carboxylic acid, sodium salt

To 0.10 g (0.301 mmol) of compound C was added 0.5 mL of 3 N aqueous KOH and 0.5 mL of EtOH, and the resulting solution was heated at 80°C for 16 h

then cooled to RT and concentrated. The residue was dissolved in water (5 mL) and brought to a pH of 7 by addition of 1 N aqueous HCl then re-concentrated. The resulting residue was redissolved in water (5 mL) and made basic (pH > 10) by adding a few drops of 1 N aqueous NaOH. The aqueous solution was concentrated, and the remaining solid treated with toluene, the toluene was evaporated and the residue dissolved in methylene chloride (~10 mL). The resulting solution was dried over sodium sulfate, filtered, and concentrated *in vacuo* to afford 0.079 g (80% yield) of the above-titled carboxylate salt D as a white solid. LC-MS (MH⁺ 306.2).

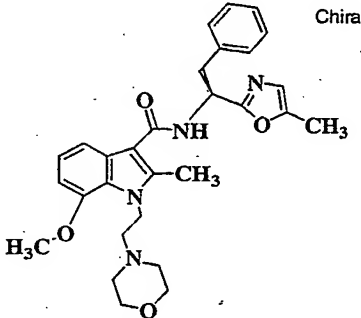
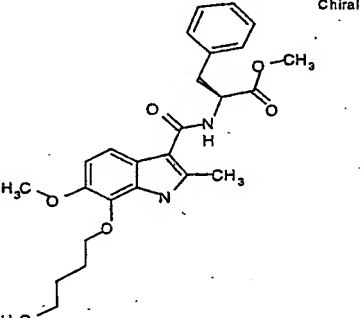
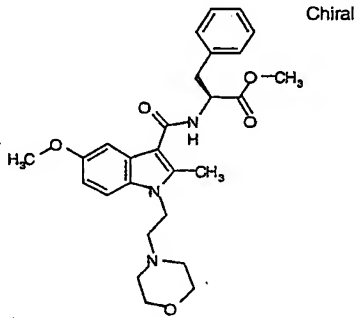
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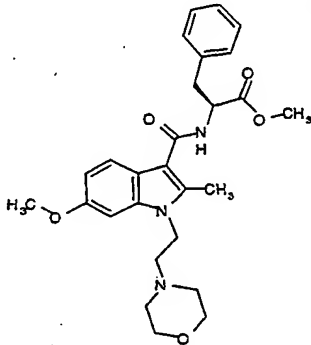
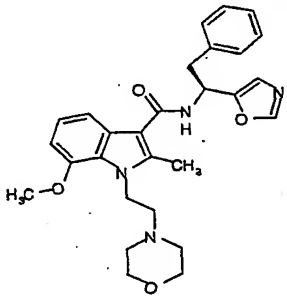
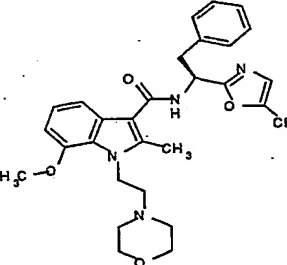
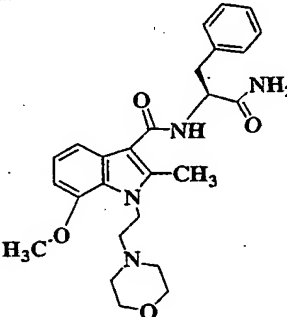
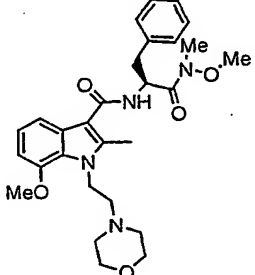
Examples 17-66

General Procedure

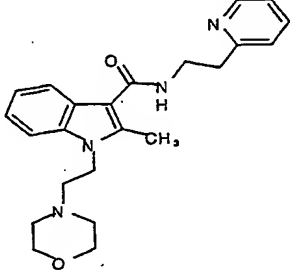
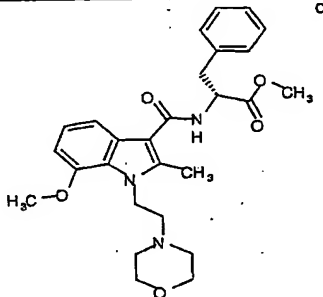
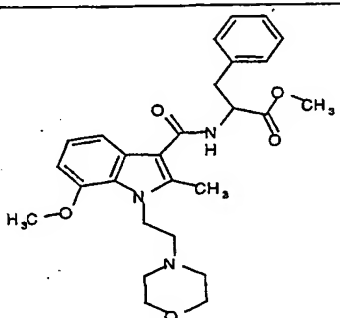
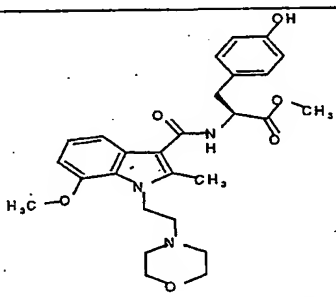
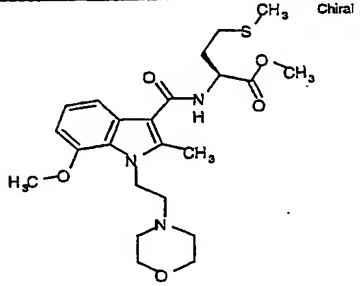
The compounds of Examples 17-66 as shown in Table 2 were prepared with the following procedure. To a solution of carboxylic acid (0.05 mmol, 15.9 mg) in 3 ml DCE was added thionyl chloride (0.15 mmol, 18 mg). The mixture was stirred at RT under N₂ for 3 h. An amine (0.11 mmol) in 2 ml DCE was added, the mixture was stirred for 2 h, and acetic anhydride (0.1 mmol) was added. After 0.5 h, the reaction was quenched with 0.5 N NaOH aqueous solution. The organic layer was subjected to cation exchange resin, the resin was washed with 20 ml MeOH, then 8 ml 2 M NH₃ in MeOH, and the basic solution was evaporated to give the following amides:

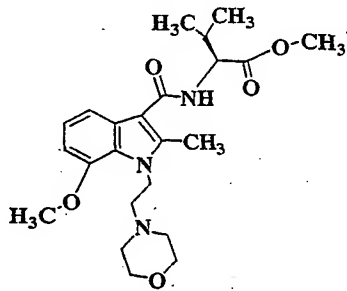
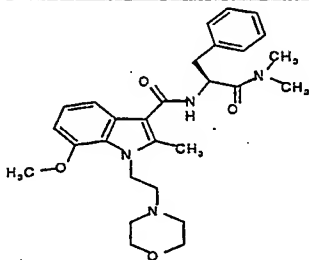
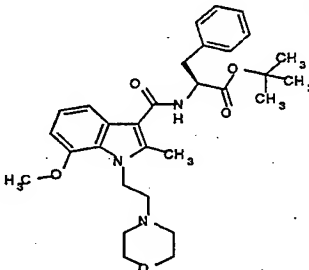
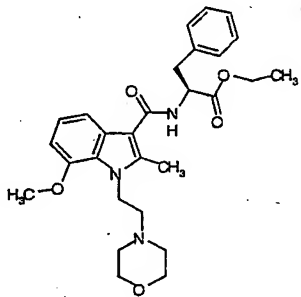
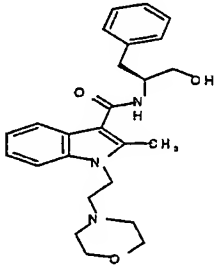
TABLE 2

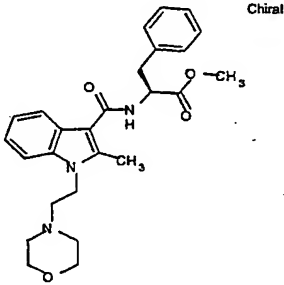
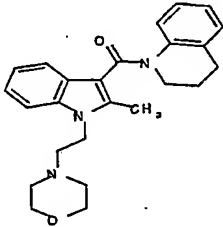
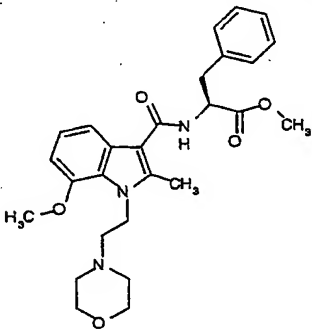
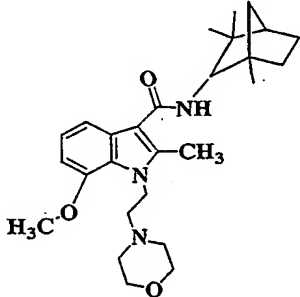
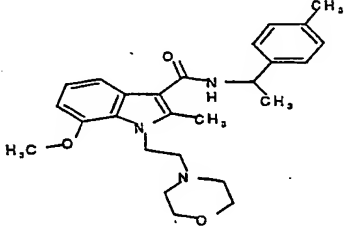
EX. NO.	STRUCTURE	COMPOUND NAME	DATA MS (M+H)/ HPLC ret. t (min) and con- ditions
17	 <p>Chiral</p>	7-Methoxy-2-methyl-N-[(1S)-1-(5-methyl-2-oxazolyl)-2-phenylethyl]-1-[2-(4-morpholinyl)ethyl]-1H-indole-3-carboxamide	503.3/ 3.14 (A)
18	 <p>Chiral</p>	N-[[6-Methoxy-2-methyl-7-(pentyloxy)-1H-indol-3-yl]carbonyl]-L-phenylalanine methyl ester	453.29/ 4.44 (A)
19	 <p>Chiral</p>	N-[[5-Methoxy-2-methyl-1-[2-(4-morpholinyl)ethyl]-1H-indol-3-yl]carbonyl]-L-phenylalanine methyl ester	480.36/ 2.94 (A)

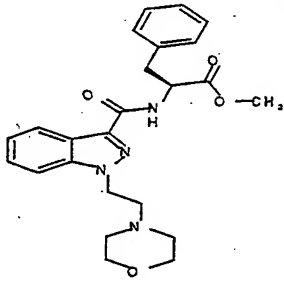
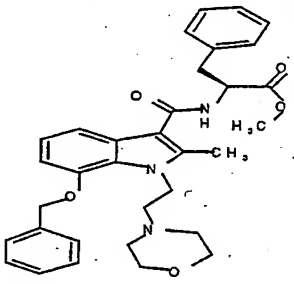
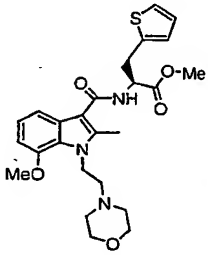
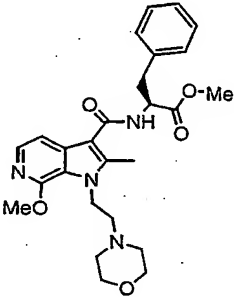
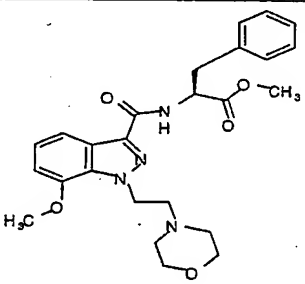
20		Chiral	N-[[6-Methoxy-2-methyl-1-[2-(4-morpholinyl)ethyl]-1H-indol-3-yl]carbonyl]-L-phenylalanine methyl ester	480.33/ 3.09 (A)
21		Chiral	7-Methoxy-2-methyl-N-[(1S)-1-(5-oxazolyl)-2-phenylethyl]-1-[2-(4-morpholinyl)ethyl]-1H-indole-3-carboxamide	489.2/2. 94 (A)
22		Chiral	7-Methoxy-2-methyl-N-[(1S)-1-(5-methyl-2-oxazolyl)-2-phenylethyl]-1-[2-(4-morpholinyl)ethyl]-1H-indole-3-carboxamide	503.3/ 3.19 (A)
23		Chiral	N-[[7-Hydroxy-2-methyl-1-[2-(4-morpholinyl)ethyl]-1H-indol-3-yl]carbonyl]-L-phenylalaninamide	465.49/ 2.73 (A)
24			N-Methoxy-N²-[[7-methoxy-2-methyl-1-[2-(4-morpholinyl)ethyl]-1H-indol-3-yl]carbonyl]-N-methyl-L-phenylalaninamide	509.50/ 3.15 (A)

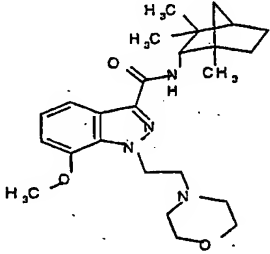
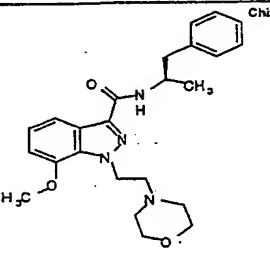
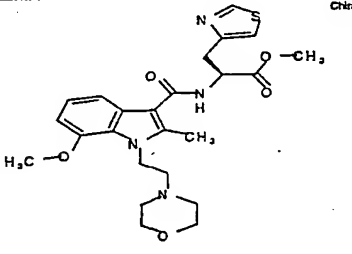
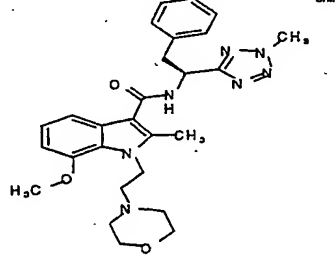
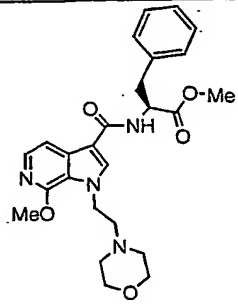
25		N-[[2,7-Dimethyl-1-[2-(4-morpholinyl)ethyl]-1H-indol-3-yl]carbonyl]-L-phenylalanine methyl ester	462.6/ 3.14 (A)
26		7-Methoxy-2-methyl-N-[(1S)-1-(3-methyl-1,2,4-oxadiazol-5-yl)-2-phenylethyl]-1-[2-(4-morpholinyl)ethyl]-1H-indole-3-carboxamide	503.6/ 2.50 (A)
27		N-[[1-Methyl-5-(pentyloxy)-1H-indol-2-yl]carbonyl]-L-phenylalanine methyl ester	333.2/ 2.77 (A)
28		2-Methyl-N-[2-(4-methylphenyl)ethyl]-1-[2-(4-morpholinyl)ethyl]-1H-indole-3-carboxamide	406.24/ 3.30 (B)
29		2-Methyl-1-[2-(4-morpholinyl)ethyl]-N-[[4-(1,2,3-thiadiazol-4-yl)phenyl]methyl]-1H-indole-3-carboxamide	462.24/ 2.82 (B)

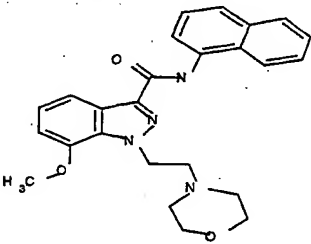
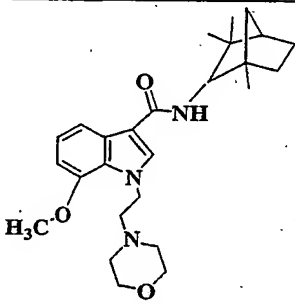
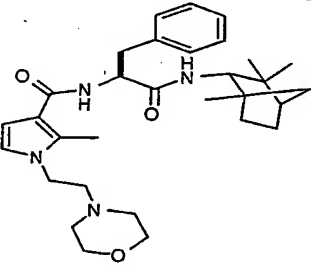
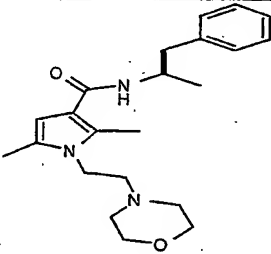
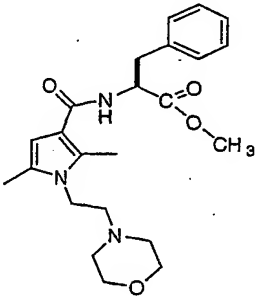
30		2-Methyl-1-[2-(4-morpholinyl)ethyl]-N-[2-(2-pyridinyl)ethyl]-1H-indole-3-carboxamide	393.26 / 1.41 (B)
31		N-[[7-Methoxy-2-methyl-1-[2-(4-morpholinyl)ethyl]-1H-indol-3-yl]carbonyl]-D-phenylalanine methyl ester	480.5 / 3.10(A)
32		N-[[7-Methoxy-2-methyl-1-[2-(4-morpholinyl)ethyl]-1H-indol-3-yl]carbonyl]-DL-phenylalanine methyl ester	480.5 / 3.10(A)
33		N-[[7-Methoxy-2-methyl-1-[2-(4-morpholinyl)ethyl]-1H-indol-3-yl]carbonyl]-L-tyrosine methyl ester	495.6 / 2.65 (A)
34		N-[[7-Methoxy-2-methyl-1-[2-(4-morpholinyl)ethyl]-1H-indol-3-yl]carbonyl]-L-methionine methyl ester	464.6 / 2.72 (A)

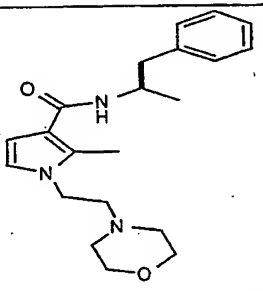
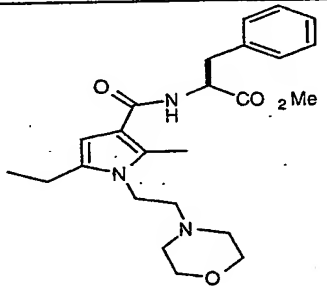
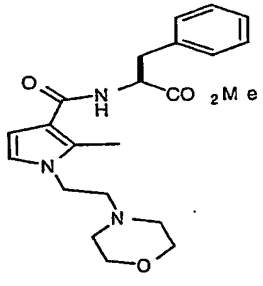
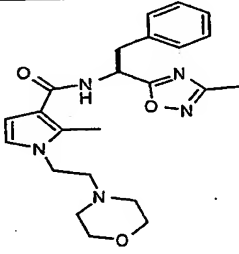
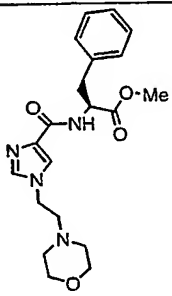
35		N-[[7-Methoxy-2-methyl-1-[2-(4-morpholinyl)ethyl]-1H-indol-3-yl]carbonyl]-3-methyl-L-valine methyl ester	446.7 3.12 (A)
36		N ² -[[7-Methoxy-2-methyl-1-[2-(4-morpholinyl)ethyl]-1H-indol-3-yl]carbonyl]-N,N-dimethyl-L-phenylalaninamide	493.4 2.97 (A)
37		N-[[7-Methoxy-2-methyl-1-[2-(4-morpholinyl)ethyl]-1H-indol-3-yl]carbonyl]-L-phenylalanine 1,1-dimethylethyl ester	422.8 3.61 (A)
38		N-[[7-Methoxy-2-methyl-1-[2-(4-morpholinyl)ethyl]-1H-indol-3-yl]carbonyl]-L-phenylalanine ethyl ester	494.4 3.28 (A)
39		(1S)-N-[1-(Hydroxymethyl)-2-phenylethyl]-2-methyl-1-[2-(4-morpholinyl)ethyl]-1H-indole-3-carboxamide	422.31 2.60 (A)

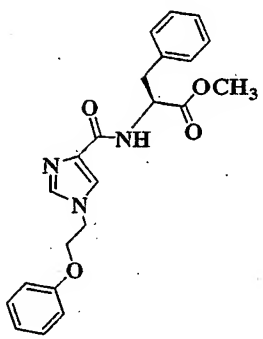
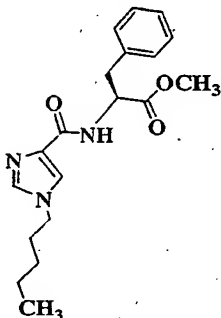
40		N-[[2-Methyl-1-[2-(4-morpholinyl)ethyl]-1H-indol-3-yl]carbonyl]-L-phenylalanine methyl ester	450.38 2.97 (A)
41		1,2,3,4-Tetrahydro-1-[[[2-methyl-1-[2-(4-morpholinyl)ethyl]-1H-indol-3-yl]carbonyl]quinoline	404.40 3.07 (A)
42		N-[[[7-Methoxy-2-methyl-1-[2-(4-morpholinyl)ethyl]-1H-indol-3-yl]carbonyl]-L-phenylalanine methyl ester	480.39 3.05 (A)
43		7-Methoxy-2-methyl-1-[2-(4-morpholinyl)ethyl]-N-(1,3,3-trimethylbicyclo[2.2.1]heptan-2-yl)-1H-indole-3-carboxamide	455.51 3.80 (A)
44		7-Methoxy-2-methyl-3-[1-(4-methylphenyl)ethyl]-1-[2-(4-morpholinyl)ethyl]-1H-indole-3-carboxamide	437.4 3.26 (A)

45		N-[1-[2-(4-morpholinyl)ethyl]-1H-indazol-3-yl]carbonyl]-L-phenylalanine methyl ester	436.5 (A)
46		N-[[7-benzyloxy-2-methyl-1-[2-(4-morpholinyl)ethyl]-1H-indol-3-yl]carbonyl]-L-phenylalanine methyl ester	555.7 3.60 (A)
47		(αS)-α-[[[7-Methoxy-2-methyl-1-[2-(4-morpholinyl)ethyl]-1H-indol-3-yl]carbonyl]amino]-2-thiophenepropanoic acid methyl ester	486.5 3.00 (A)
48		N-[[7-Methoxy-2-methyl-1-[2-(4-morpholinyl)ethyl]-6-aza-1H-indol-3-yl]carbonyl]-L-phenylalanine methyl ester	480.6 2.58 (A)
49		N-[[7-Methoxy-1-[2-(4-morpholinyl)ethyl]-1H-indazol-3-yl]carbonyl]-L-phenylalanine methyl ester	466.5 (A)

50		7-Methoxy-1-[2-(4-morpholinyl)ethyl]-N-(1,3,3-trimethylbicyclo[2.2.1]heptan-2-yl)-1H-indazol-3-carboxamide	440.6 (A)
51		N-[[7-Methoxy-1-[2-(4-morpholinyl)ethyl]-1H-indazol-3-yl]carbonyl]-R-amphetamine	422.5 (A)
52		(αS)-α-[[[7-Methoxy-2-methyl-1-[2-(4-morpholinyl)ethyl]-1H-indol-3-yl]carbonyl]amino]-2-thiazolepropanoic acid methyl ester	487.2 2.44 (A)
53		7-Methoxy-2-methyl-N-[(1S)-1-(3-methyl)-tetrazolyl]-2-phenylethyl]-1-[2-(4-morpholinyl)ethyl]-1H-indole-3-carboxamide and 7-Methoxy-2-methyl-N-[(1S)-1-(2-methyl)-tetrazolyl]-2-phenylethyl]-1-[2-(4-morpholinyl)ethyl]-1H-indole-3-carboxamide (1:1 mixture)	503.6 (A)
54		N-[[7-Methoxy-1-[2-(4-morpholinyl)ethyl]-1H-indol-3-yl]carbonyl]-L-phenylalanine methyl ester	465.6 (A)

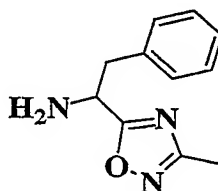
55		N-[[7-Methoxy-1-[2-(4-morpholinyl)ethyl]-1H-indazol-3-yl]carbonyl]-1-naphthyl amide	430.5 (A)
56		7-Methoxy-1-[2-(4-morpholinyl)ethyl]-N-(1,3,3-trimethylbicyclo[2.2.1]heptan-2-yl)-1H-indole-3-carboxamide	439.6 (A)
57		2-Methyl-1-[2-(4-morpholinyl)ethyl]-N-(1,3,3-trimethylbicyclo[2.2.1]heptan-2-yl)-1H-pyrrole-3-carboxamide	374.41 3.28 (A)
58		2,5-Dimethyl-N-[(1R)-1-methyl-2-phenylethyl]-1-[2-(4-morpholinyl)ethyl]-1H-pyrrole-3-carboxamide	370.28 2.64 (A)
59		N-[[2,5-Dimethyl-1-[2-(4-morpholinyl)ethyl]-1H-pyrrol-3-yl]carbonyl]-L-phenylalanine methyl ester	414.26 2.49 (A)

60		2-Methyl-N-[(1R)-1-methyl-2-phenylethyl]-1-[2-(4-morpholinyl)ethyl]-1H-pyrrole-3-carboxamide	356.31 2.46 (A)
61		N-[[5-Ethyl-2-methyl-1-[2-(4-morpholinyl)ethyl]-1H-pyrrol-3-yl]carbonyl]-L-phenylalanine methyl ester	428.29 2.88 (A)
62		N-[[2-Methyl-1-[2-(4-morpholinyl)ethyl]-1H-pyrrol-3-yl]carbonyl]-L-phenylalanine methyl ester	400.28 2.48 (A)
63		2-Methyl-N-[(1S)-1-(3-methyl-1,2,4-oxadiazol-5-yl)-2-phenylethyl]-1-[2-(4-morpholinyl)ethyl]-1H-pyrrole-3-carboxamide	504.35 3.10 (A)
64		N-[[1-[2-(4-morpholinyl)ethyl]-1H-imidazol-4-yl]carbonyl]-L-phenylalanine methyl ester	387.30 2.33 (A)

65		Chiral	N-[[1-(2-Phenoxyethyl)-1H-imidazol-4-yl]carbonyl]-L-phenylalanine methyl ester	394.25 2.87 (B)
66		Chiral	N-[(1-Pentyl-1H-imidazol-4-yl)carbonyl]-L-phenylalanine methyl ester	344.29 3.39 (A)

Example 67

(R)-1-(3-Methyl-[1,2,4]oxadiazol-5-yl)-2-phenylethylamine



5

A. (R)-[1-(3-methyl-[1,2,4]oxadiazol-5-yl)-2-phenylethyl] carbamic acid tertbutyl ester

10

To a solution of *N*-Boc-L-phenylalanine (2.0 g, 7.5 mmol) in CH₂Cl₂ (20 mL) at 0°C was added DCC (780 mg, 3.8 mmol) in CH₂Cl₂ (20 mL) via cannula. The reaction mixture was stirred for 1h, the precipitate filtered off, and the filtrate concentrated to dryness. Acetamidoxime (195 mg, 2.64 mmol) and pyridine (20 mL) were added and the reaction mixture heated at reflux for 1.5 h and then at RT for 16 h. The reaction mixture was poured into EtOAc (50 mL) and washed with 10% citric

15

acid (3 x 25 mL). The organic layer was dried over Na₂SO₄, filtered, and concentrated *in vacuo*. Purification by column chromatography (25% EtOAc/hex) furnished (R)-[1-(3-methyl-[1,2,4]oxadiazol-5-yl)-2-phenylethyl] carbamic acid *tert*butyl ester (790 mg, 99% yield). 304.22, M+H.

5

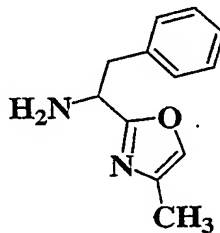
B. (R)-1-(3-methyl-[1,2,4]oxadiazol-5-yl)-2-phenylethylamine

To the carbamate from step A was added 4 N HCl in dry dioxane (10 mL) and the mixture was stirred for 4 h. The reaction mixture was concentrated to dryness, dissolved in 10% HCl (100 mL) and washed with CH₂Cl₂ (2 x 50 mL). The aqueous
10 layer was made basic with 3N NaOH and extracted with CH₂Cl₂ (3 x 50 mL). The combined organic extracts were dried over Na₂SO₄, filtered, and concentrated *in vacuo* to give the above-titled Example 67 (506 mg, 94% yield). 204.18, M+H.

Example 68

15

4-Methyl-2-[[1-phenyl-2-L-amino]ethyl]oxazole



A. CBZ-L-Phenyl alanyl-1-amino-2-propanol

CBZ-L-Phenyl alanine (1 mmol, 300 mg), BOP reagent (1.5 mmol, 660 mg), NMM (5 mmol, 570 mg) and 1-amino-2-propanol (1.5 mmol, 113 mg) were mixed in
20 20 ml DMF. The mixture was stirred and heated to 50°C overnight, quenched with EtOAc (30 ml), washed with NaHCO₃ (aq. Sat.), NaHSO₄ (aq. Sat.) and water, and dried over MgSO₄ to give 330 mg of the above-titled compound A.

B. CBZ-L-Phenyl alanyl-1-amino-2-oxo-propane

25 0.2 M COCl₂ in CH₂Cl₂ was added into 5 ml methylene chloride and cooled to -78°C, then 0.5 ml DMSO was added dropwise and the mixture was stirred for 0.5 h at -78°C. 330 mg crude product from step A dissolved in 2ml DMSO and 4 ml methylene chloride were added, and the reaction mixture was stirred for one hour at

-78°C, then stirred at RT for one hour. The mixture was added into 20 ml methylene chloride, washed with NaHCO₃ and NaHSO₄ and water, dried over MgSO₄, and the solvent was evaporated to give 340 mg of the above-titled compound B as a crude product.

5

C. 4-Methyl-2-[[1-phenyl-2-(CBZ)-L-amino]ethyl]oxazole

Compound B was dissolved in POCl₃ (10ml), and the mixture was stirred at RT under N₂ overnight. The reaction mixture was carefully poured into iced 1N NaOH solution, extracted with EtOAc, washed with brine, dried over MgSO₄, and the solvent evaporated to give 312 mg of crude compound C.

10

D. 4-Methyl-2-[[1-phenyl-2-L-amino]ethyl]oxazole

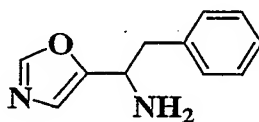
312 mg of compound C was dissolved in MeOH followed by hydrogenation by 10% Pd/C as a catalyst at RT overnight. The mixture was filtered and evaporated. The crude product was purified by cation exchange resin to give 100 mg of compound D (Example 68) as a yellow oil.

15

Example 69

4- [[1-Phenyl-2-L-amino]ethyl]oxazole

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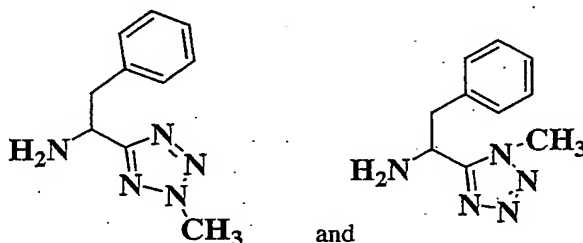
A solution of trimethylsilylmethyl isocyanide (500 mg, 4.4 mmol) was cooled to -78°C in N₂. N-BuLi (1.6 M, 2.9 ml, 4.6 mmol) was added over 10 min, the mixture was stirred for 15 min at -78°C, and a solution of Boc-L-phenylalanine (490 mg, 1.80 mmol) in THF (2 mL) was introduced over 10 min. Stirring was continued at -78°C for 10 min and the reaction was warmed to 0°C for 15 min. After AcOH (0.26 ml, 4.6 mmol) was added, it was concentrated to give 4-[[1-Phenyl-2-L-amino]ethyl]oxazole (crude, 300 mg). This compound was dissolved in methylene chloride (5 ml), 4N HCl in 4ml dioxane was added, and the mixture was stirred at RT

30

for 3 h. Evaporation of the solvent, methylene chloride addition, and evaporation gave the above-titled compound (100 mg, HCl form).

Example 70

1-[2-Phenyl-1-L-amino]ethyl-2-methyl tetrazole and
1-[2-Phenyl-1-L-amino]ethyl-3-methyl tetrazole (1:1)



A. Boc-L-Phenylalanyl amide

i-Butylchloroformate (0.66 ml, 5 mmol) was added to a solution of Boc-phenylalanine (1.38 g, 5 mmol) and NMM (0.55 ml, 5 mmol) in 25 ml of methylene chloride at -20°C . After stirring for 20 min. at -20°C , 25 ml of 2M ammonia/MeOH was added. After 5 min., the reaction mixture was partitioned between EtOAc (100 ml) and water (100 ml). The organic layer was washed with saturated KHSO_4 solution (100 ml), water (100 ml), saturated NaHCO_3 solution (100 ml) and brine (100 ml). Drying (over MgSO_4) and concentration afforded 1.33 g (99%) of product A as a white solid.

B. [[2-Phenyl-1-L-(tert-butyloxy)amino]ethyl]nitrile

A mixture of compound A (1.30 g, 4.9 mmol) and (methoxycarbonylsulfamoyl)-triethylammonium hydroxide, inner salt (1.7 g, 7.4 mmol) in 50 ml of THF was stirred 1 hr at RT. After removing the THF *in vacuo*, the residue was filtered through a 5 x 5 cm plug of silica gel and washed with EtOAc:Hex (1:1). The filtrate was concentrated to afford 1.19 g (99%) of compound B as a white solid.

C. 1-[[2-Phenyl-1-L-(tert-butyloxy)amino]ethyl]-tetrazole

To a cooled (-78°C) solution of 1.8M diethylaluminum chloride in toluene (8.6 ml, 15 mmol) was added dropwise over 15 min. a solution of compound B (1.19

g, 4.8 mmol) and azidotrimethylsilane (2.4 ml, 17 mmol) in 20 ml of methylene chloride. After slowly warming to RT, the reaction mixture was stirred for 18 hr. 5% AcOH/MeOH (30 ml) was added in small portions with caution to quench the reaction mixture. After addition was complete, the resulting mixture was partitioned between EtOAc (150 ml) and water (150 ml). The organic layer was washed with water (150 ml) and brine (150 ml). Drying (over MgSO_4) and concentration afforded 884 mg (64%) of compound C as a white powder.

D. 3 and 2-Methyl-1-[[2-phenyl-1-L-(tert-butyloxy)amino]ethyl]-tetrazole

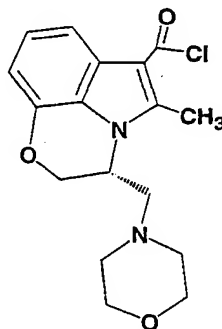
A mixture of compound C (400 mg, 1.4 mmol), K_2CO_3 (250 mg, 1.8 mmol) and iodomethane (256 mg, 1.8 mmol) in 2 ml of DMF was stirred for 3 h at RT. After partitioning the reaction mixture between EtOAc (100 ml) and water (100 ml), the organic layer was washed with water (2 x 100 ml) and brine (100 ml). Drying (MgSO_4) and concentration afforded 405 mg (96%) of D, a 1:1 mixture of the above-titled compounds as a light yellow solid.

E. 1-[2-phenyl-1-L-amino]ethyl-2 and 3-methyl tetrazole

A mixture of D (400 mg, 1.3 mmol) and 4N HCl/dioxane (3 ml; 12 mmol) in 10 ml of EtOAc was stirred for 18 hr at RT. Concentration and trituration with ethyl ether afforded 300 mg (96%) of a 1:1 mixture of the compounds of Example 70 as the hydrochloride salt.

Example 71

(3S)-2,3-Dihydro-5-methyl-3-(4-morpholinylmethyl)-N-pyrrolo [1,2,3-de]-1,4-benzoxazine-6-carboxylic acid chloride



A. 2-Methyl-7-hydroxyindole

To 2-methyl-7-methoxyindole (5 g, 34 mmol) in CH_2Cl_2 (100mL) cooled in an ice bath was slowly added neat BBr_3 (9.5mL, 100 mmol). The reaction mixture was
5 allowed to warm to RT and then stirred for an additional 12h. After cooling to -10°C , the reaction was quenched by the addition of MeOH (32mL) and the solvent removed *in vacuo*. The residue was triturated with Et_2O and filtered to give 6.86 g (95%) of compound A as light brown solid as the HBr salt. HPLC ret. t: 2.7 min (A).

10 B. 2-Methyl-7-((R)-2,3-oxo)propyloxy indole

To compound A (2.8 g, 20 mmol) in THF (40 mL) cooled to 0°C was added freshly distilled (R)-(+)-glycidol (2.7 mL, 41 mmol) and PPh_3 (12 g, 45 mmol) followed by slow addition of DEAD (7.4 mL, 47.0 mmol). The reaction was allowed to warm to RT and stirred for an additional 12h, then the solvent was removed *in*
15 *vacuo* and the crude mixture purified by column chromatography to give 1.74 g (42.4%) of compound B as a thick oil. HPLC ret. t: 3.3 min. Compound B also was obtained by reaction of compound A in EtOH with (R)-(-)-epichlorohydrin using K_2CO_3 as base at 40°C to give 73% of product B after purification.

20 C. 2-Methyl-7-(3-morpholino-2-(S)-hydroxy)propyloxyindole

To compound B (1.7 g, 8.6 mmol) in THF (5 mL) was added morpholine (8 mL) and the mixture heated to 60°C for 1.5h. After cooling to RT, water was added and extracted with EtOAc. The EtOAc was washed with saturated NaCl and dried over MgSO_4 . The solvent was removed *in vacuo* to a small volume and the product
25 was crystallized with addition of Et_2O . Filtration gave 1.65 g (67%) of compound C as a pale solid. HPLC ret. t: 2.31 min (A).

D. 2-Methyl-7-[3-morpholino-2(S)-(methylsulfonyl)]propyloxyindole

To compound C (1.6 g, 5.48 mmol) in CH_2Cl_2 (30 mL) cooled to 0°C was
30 added TEA (1.5 mL, 11 mmol) followed by slow addition of methanesulfonyl chloride (0.6mL, 6.0 mmol). The reaction was stirred at 0°C for 0.5 h, then added to ice cold water and extracted with CH_2Cl_2 . The organic layer was washed with

saturated NaCl then dried over MgSO₄. The solvent was removed *in vacuo*, then anhydrous THF was added and removed *in vacuo* 2 times. The crude material was used immediately in the next step with no further purification. HPLC ret. t: 2.6 min (A).

5

E. (3S)-2,3-Dihydro-5-methyl-3-(4-morpholinylmethyl)-N-pyrrolo[1,2,3-de]-1,4-benzoxazine

To NaH (400 mg, 17 mmol) in anhydrous THF (50 mL) cooled in an ice bath was added crude compound D in THF (50 mL) followed by the addition of DMF (20 mL). The reaction was allowed to slowly warm to RT then stirred for an additional 1h. The reaction mixture was cooled in an ice bath, then quenched with HOAc and the solvent removed *in vacuo*. Water was added to the residue which was neutralized with NaOH then filtered to give 1.3 g (86.5%; 94.96%ee by chiral HPLC) of compound E as a crystalline solid. HPLC ret. t: 2.207 min (A).

15

F. (3S)-2,3-Dihydro-5-methyl-3-(4-morpholinylmethyl)-N-pyrrolo[1,2,3-de]-1,4-benzoxazine-6-trichloromethyl ketone

To compound E (1.18 g, 4.33 mmol) in DCE (24 mL) was added trichloroacetyl chloride (1.45 mL, 13.0 mmol), and then the mixture was heated to reflux for 1.5h. After the reaction was cooled in an ice bath, Et₂O was added and the precipitate collected by filtration to give 1.83 g (93%) of compound F as pale solid as the HCl salt. HPLC ret. t: 3.1 min (A).

20

G. (3S)-2,3-Dihydro-5-methyl-3-(4-morpholinylmethyl)-N-pyrrolo[1,2,3-de]-1,4-benzoxazine-6-carboxylic acid

To compound F (1.8 g, 4.0 mmol) in THF (40 mL) was added NaOH (2.77 mL, 50%aq), and the mixture stirred at RT for 1h. After the solvent was removed *in vacuo*, water was added and extracted with CH₂Cl₂. The aqueous layer was brought to pH 6 with HCl and the solid collected by filtration to give 0.97 g (76.5%) of compound G as a pale solid. HPLC ret. t: 1.96 min.

30

H. (3S)-2,3-Dihydro-5-methyl-3-(4-morpholinylmethyl)-N-pyrrolo[1,2,3-de]-1,4-benzoxazine-6-carboxylic acid chloride

To compound G (0.35 g, 1.1 mmol) in CH_2Cl_2 (10 mL cooled in an ice bath) was slowly added oxalyl chloride (0.39 mL, 4.42 mmol) followed by 1 drop DMF. The reaction was allowed to warm to RT then stirred for an additional 0.5h. Et_2O was added to precipitate the product as the HCl salt which was collected by filtration to give 410 mg (99.8%) of Example 71 as a light brown solid.

Examples 72-82

General Scheme for the preparation of tricyclic amides

The compounds of Examples 72-82, wherein $-\text{NR}_1\text{R}_2$ have the values listed in Table 3, were prepared as follows. To Example 71 (40 mg, 0.11 mmol) in THF (0.7 mL) was added TEA (60 μL , 0.43 mmol) followed by the appropriate amine (25.6 mg, 0.118 mmol), and the mixture was stirred at RT for 1h. The reaction was diluted with EtOAc and extracted with water. The EtOAc was dried over Na_2SO_4 and then the solvent removed *in vacuo*. The residue was dissolved in CH_2Cl_2 and 4N HCl in dioxane was added followed by Et_2O . The product was isolated by filtration as the HCl salt.

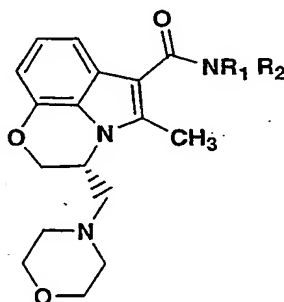


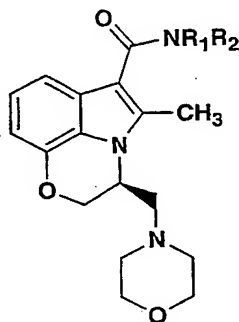
TABLE 3

EXAMPLE NO.	$-\text{NR}_1\text{R}_2$	COMPOUND NAME	DATA MS ($\text{M}+\text{H}^+$)
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72		(3R)-2,3-Dihydro-5-methyl-3-(4-morpholinylmethyl)-N-(2,2,6,6-tetramethylcyclohexyl)pyrrolo[1,2,3-de]-1,4-benzoxazine-6-carboxamide	454.39
73		N-[[[(3R)-2,3-Dihydro-5-methyl-3-(4-morpholinylmethyl)pyrrolo[1,2,3-de]-1,4-benzoxazin-6-yl]carbonyl]-L-phenylalanine methyl ester	478.33
74		N-[[[(3R)-2,3-Dihydro-5-methyl-3-(4-morpholinylmethyl)pyrrolo[1,2,3-de]-1,4-benzoxazin-6-yl]carbonyl]-L-tyrosine methyl ester	494.31
75		(3R)-N-[2-(4-Aminophenyl)ethyl]-2,3-dihydro-5-methyl-3-(4-morpholinylmethyl)pyrrolo[1,2,3-de]-1,4-benzoxazine-6-carboxamide	435.29
76		(3R)-N-(2,2-Dimethylcyclopentyl)-2,3-dihydro-5-methyl-3-(4-morpholinylmethyl)pyrrolo[1,2,3-de]-1,4-benzoxazine-6-carboxamide	412.31
77		(3R)-2,3-Dihydro-5-methyl-N-[2-methyl-1-(1-methylethyl)propyl]-3-(4-morpholinylmethyl)pyrrolo[1,2,3-de]-1,4-benzoxazine-6-carboxamide	414.32
78		N-[[[(3R)-2,3-Dihydro-5-methyl-3-(4-morpholinylmethyl)pyrrolo[1,2,3-de]-1,4-benzoxazin-6-yl]carbonyl]-3-methyl-L-valine methyl ester	444.32
79		(3R)-2,3-Dihydro-5-methyl-3-(4-morpholinylmethyl)-N-(1,3,3-trimethylbicyclo[2.2.1]heptan-2-yl)pyrrolo[1,2,3-de]-1,4-benzoxazine-6-carboxamide	452.37

Examples 80-82

The following compounds were prepared following the procedure for Examples 72-79 except the (S)-(-)-glycidol was utilized.

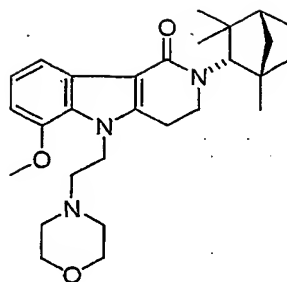


EX. NO.	-NR ₁ R ₂	COMPOUND NAME	DATA MS (M+H ⁺)
80		N-[[[(3S)-2,3-Dihydro-5-methyl-3-(4-morpholinylmethyl)pyrrolo[1,2,3-de]-1,4-benzoxazin-6-yl]carbonyl]-L-phenylalanine methyl ester	478.34
81		(3S)-2,3-Dihydro-5-methyl-3-(4-morpholinylmethyl)-N-(2,2,6,6-tetramethylcyclohexyl)pyrrolo[1,2,3-de]-1,4-benzoxazine-6-carboxamide	454.39
82		(3S)-2,3-Dihydro-5-methyl-3-(4-morpholinylmethyl)-N-(1,3,3-trimethylbicyclo[2.2.1]heptan-2-yl)pyrrolo[1,2,3-de]-1,4-benzoxazine-6-carboxamide	452.37

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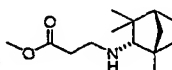
Example 83

2,3,4,5-Tetrahydro-6-methoxy-5-[2-(4-morpholinyl)ethyl]-2-[(1S,2S)-1,3,3-trimethylbicyclo[2.2.1]heptan-2-yl]-1H-pyrido[4,3-b]indol-1-one



A. 3-[[[(1S,2S)-1,3,3-Trimethylbicyclo[2.2.1]heptan-2-yl]amino]propanoic acid methyl ester

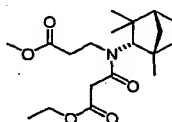
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A solution of (S)-fenchyl amine.HCl (1.0 g, 5.32 mmol) in dry MeOH was cooled to 0°C in a resealable tube. TEA (0.75 mL, 5.32 mmol) was added followed by methyl acrylate (0.527 mL, 5.9 mmol). The tube was sealed and the mixture stirred at RT for 5 days. The crude reaction mixture was concentrated *in vacuo* and used without further purification in the next step. 240.2 (M+H), ret. t: 1.35 min (B).

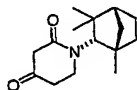
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B. 3-Oxo-3-[(3-methoxy-3-oxopropyl)][(1S,2S)-1,3,3-trimethylbicyclo[2.2.1]heptan-2-yl]amino]propanoic acid ethyl ester



To a solution of the methyl ester from step A in CH₂Cl₂ (25 mL) at 0°C was added TEA (1.11 mL, 8 mmol), followed slowly by ethyl 2-chloropropionate (0.84 mL, 5.85 mmol). The reaction vessel was allowed to warm to RT slowly. After 4h, 15% K₂CO₃ (6 mL) was added and the reaction stirred rapidly for 15 min. The layers were separated and the organic layer washed with 1N HCl (15 mL). The organic layer was dried over Na₂SO₄, filtered, and concentrated *in vacuo* to an oil. The residue was purified by column chromatography (20% EtOAc/hex then 50% EtOAc/hex) to furnish the above compound B as a clear oil (1.15 g, 62% yield overall). 353.2 (M+H), ret. t.: 3.96 min (A).

C. 1-[(1S,2S)-1,3,3-Trimethylbicyclo[2.2.1]heptan-2-yl]-2,4-piperidinedione

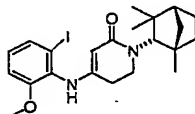


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A suspension of NaH (130 mg, 60% in oil) in cyclohexane (7 mL) was heated at reflux. A solution of the ethyl ester from step B (500 mg, 1.41 mmol) in toluene (1 mL) was added dropwise via syringe over 1 h. The reaction mixture was heated at reflux an additional 5h, and then allowed to cool and stir overnight. The solid was filtered off and washed with hex (2 mL). The solid was then added to 10% AcOH (11.3 mL) and heated at reflux for 4 h. The reaction mixture was allowed to cool and neutralized to pH 7 with dilute NaHCO₃. The aqueous solution was extracted with CH₂Cl₂ (3x35 mL), combined, dried (Na₂SO₄), and concentrated *in vacuo*. The residue was purified by column chromatography (25% EtOAc/hex then 40% EtOAc/hex) to furnish the above compound C (177 mg, 50% yield). 250.2 (M+H), ret. t: 3.49 min (A).

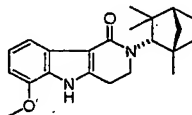
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D. 5,6-Dihydro-4-[(2-iodo-6-methoxyphenyl)amino]-1-[(1S,2S)-1,3,3-trimethylbicyclo[2.2.1]heptan-2-yl]-2(1H)-pyridinone



To a solution of 2-iodo-6-methoxy aniline and the ketone from step C in benzene (3 mL) was added TsOH.H₂O, and the mixture was heated at reflux with removal of water for 6h. The reaction mixture was cooled, poured into EtOAc (40 mL), and washed with water (15 mL). The organic layer was dried (Na₂SO₄), filtered, and concentrated *in vacuo*. The residue was purified by column chromatography (25% EtOAc/hex then 50% EtOAc/hex) to furnish the above compound D (104 mg, 61% yield).

- E. 2,3,4,5-Tetrahydro-6-methoxy-2-[(1S,2S)-1,3,3-trimethylbicyclo[2.2.1]heptan-2-yl]-1H-pyrido[4,3-b]indol-1-one



5

To the iodo-substituted pyridinone from step D (75 mg, 0.156 mmol) in a resealable tube was added 0.30 mL of a solution of Pd(OAc)₂ (20.1 mg, 0.089 mmol) and tri-ortho tolylphosphine (59 mg, 0.19 mmol) in DMF (0.89 mL). The mixture was degassed via three freeze pump thaw cycles, TEA was added (0.044 mL, 0.312 mmol), and the tube was sealed under N₂. The reaction tube was heated to 120°C for 6h. The reaction tube was cooled, EtOAc was added (2 mL), and the mixture was stirred in open air for 1 h. The reaction was directly purified by column chromatography (105% EtOAc/hex then 33% EtOAc/hex) to furnish the above compound E (54 mg, 99% yield). 353.3 (M+H), ret. t: 3.65 min (A).

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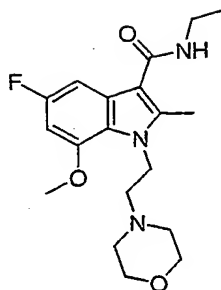
- F. 2,3,4,5-Tetrahydro-6-methoxy-5-[2-(4-morpholinyl)ethyl]-2-[(1S,2S)-1,3,3-trimethylbicyclo[2.2.1]heptan-2-yl]-1H-pyrido[4,3-b]indol-1-one

To a solution of the indole from step E (15 mg, 0.042 mmol) in DMF (0.25 mL) was added 2-chloroethyl morpholine.HCl (9.5 mg, 0.051 mmol) and NaH (5.2 mg, 60% in oil), and the reaction was heated to 60°C overnight. The reaction was cooled to RT, and water (2 mL) was added dropwise. The solids were collected to yield the above-titled compound (Example 83) (>98% purity, HPLC) (16.5 mg, 83% yield). 466.5 (M+H), ret. t: 3.46 min (A). (See also Example 2, step A).

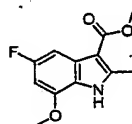
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Example 84

N-Ethyl-5-fluoro-7-methoxy-2-methyl-1-[2-(4-morpholinyl)ethyl]-1H-indole-3-carboxamide



- A. 5-Fluoro-7-methoxy-2-methyl-1H-indole-3-carboxylic acid methyl ester

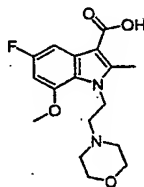


5

The above compound A was prepared from 2-bromo-4-fluoro-6-methoxy aniline and methyl acetoacetate according to the general procedure described above for Example 83, steps D and E. 238.0 (M+H), ret t: 3.64 min (A).

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- B. 5-Fluoro-7-methoxy-2-methyl-1-[2-(4-morpholinyl)ethyl]-1H-indole-3-carboxylic acid



15

The above compound B was prepared according to the procedure in Example 2, steps A and B. 337.2 (M+H), rt 1.74 (A). The compound of Example 84 was then prepared from compound B according to the procedure described above for Examples 3-12. 364.3 (M+H), ret. t: 1.39 min (A).

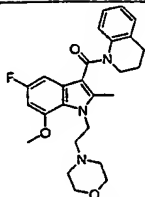
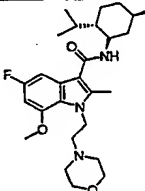
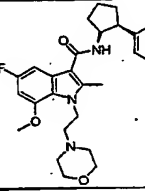
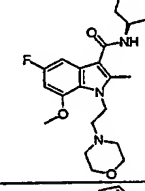
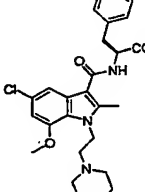
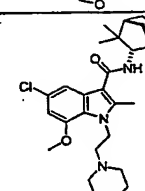
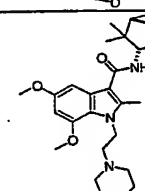
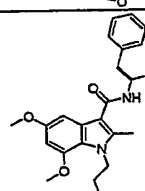
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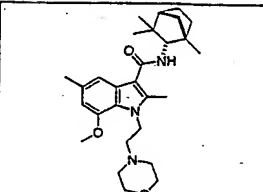
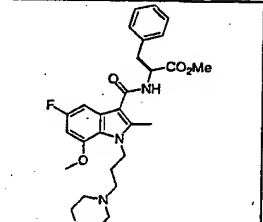
Examples 85-108

Compounds of Examples 85-108 as shown in Table 5 were prepared following the same or similar procedure as described for Example 84.

TABLE 5

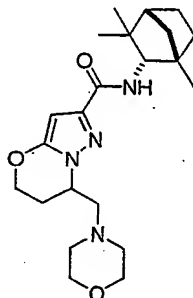
EX. NO.	STRUCTURE	COMPOUND NAME	DATA (M+H)/ HPLC ret. t. (min.) and conditions
85		N-[[5-Fluoro-7-methoxy-2-methyl-1-[2-(4-morpholinyl)ethyl]-1H-indol-3-yl]carbonyl]-L-phenylalanine methyl ester	498.2/ 3.25 (A)
86		5-Fluoro-7-methoxy-N,2-dimethyl-1-[2-(4-morpholinyl)ethyl]-1H-indole-3-carboxamide	350.3/ 0.89 (B)
87		5-Fluoro-7-methoxy-2-methyl-1-[2-(4-morpholinyl)ethyl]-N-[(1S,2S)-1,3,3-trimethylbicyclo[2.2.1]heptan-2-yl]-1H-indole-3-carboxamide	472.4/ 3.22 (A)
88		5-Fluoro-7-methoxy-N-(2-methoxyphenyl)-2-methyl-1-[2-(4-morpholinyl)ethyl]-1H-indole-3-carboxamide	442.3/ 2.63 (A)
89		5-Fluoro-7-methoxy-2-methyl-N-(2-methylcyclohexanyl)-1-[2-(4-morpholinyl)ethyl]-1H-indole-3-carboxamide	432.3/ 1.63 (B)
90		N-(2-Ethylphenyl)-5-fluoro-7-methoxy-2-methyl-1-[2-(4-morpholinyl)ethyl]-1H-indole-3-carboxamide	440.3/ 1.52 (B)

99		1-[[5-Fluoro-7-methoxy-2-methyl-1-[2-(4-morpholinyl)ethyl]-1H-indol-3-yl]carbonyl]-1,2,3,4-tetrahydroquinoline	452.5/ 2.08 (A)
100		5-Fluoro-7-methoxy-2-methyl-N-[(1R,2S,5R)-5-methyl-2-(1-methylethyl)cyclohexanyl]-1-[2-(4-morpholinyl)ethyl]-1H-indole-3-carboxamide	474.4/ 1.88 (B)
101		5-Fluoro-7-methoxy-2-methyl-1-[2-(4-morpholinyl)ethyl]-N-[(1S,2S)-2-phenylcyclopentyl]-1H-indole-3-carboxamide	480.3 2.28 (A)
102		5-Fluoro-7-methoxy-2-methyl-N-[(1R)-1-methylpropyl]-1-[2-(4-morpholinyl)ethyl]-1H-indole-3-carboxamide	392.3 1.24 (B)
103		N-[[5-Chloro-7-methoxy-2-methyl-1-[2-(4-morpholinyl)ethyl]-1H-indol-3-yl]carbonyl]-L-phenylalanine methyl ester	514.3 3.35 (A)
104		5-Chloro-7-methoxy-2-methyl-1-[2-(4-morpholinyl)ethyl]-N-[(1S,2S)-1,3,3-trimethylbicyclo[2.2.1]heptan-2-yl]-1H-indole-3-carboxamide	488.4/ 4.00 (A)
105		5,7-Dimethoxy-2-methyl-1-[2-(4-morpholinyl)ethyl]-N-[(1S,2S)-1,3,3-trimethylbicyclo[2.2.1]heptan-2-yl]-1H-indole-3-carboxamide	484.4/ 2.46 (A)
106		N-[[5,7-Dimethoxy-2-methyl-1-[2-(4-morpholinyl)ethyl]-1H-indol-3-yl]carbonyl]-L-phenylalanine methyl ester	510.3/ 3.79 (A)

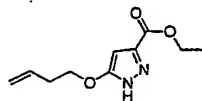
107		7-Methoxy-2,5-dimethyl-1-[2-(4-morpholinyl)ethyl]-N-[(1S,2S)-1,3,3-trimethylbicyclo[2.2.1]heptan-2-yl]-1H-indole-3-carboxamide	468.4/ 3.52 (A)
108		5-Fluoro-7-methoxy-2-methyl-1-[3-(4-morpholinyl)propyl]-N-[(1S,2S)-1,3,3-trimethylbicyclo[2.2.1]heptan-2-yl]-1H-indole-3-carboxamide	486.4/ 3.34 (A)

Example 109

6,7-Dihydro-7-(4-morpholinylmethyl)-N-[(1S,2S)-1,3,3-trimethylbicyclo[2.2.1]heptan-2-yl]-5H-pyrazolo[5,1-b][1,3]oxazine-2-carboxamide



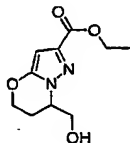
A. 5-(3-Butenyloxy)-1H-pyrazole-3-carboxylic acid ethyl ester



To a solution of ethyl 2-pyrazolin-5-one 3 carboxylate (537 mg, 3.43 mmol) and 4 bromo-1-butene (0.35 mL, 3.44 mmol) in MeCN (15 mL) was added Cs₂CO₃ (1.12 g, 3.44 mmol), and the reaction mixture was heated to 60°C overnight. The reaction mixture was cooled and diluted with EtOAc (75 mL), and washed with water (2x35 mL) and brine (35 mL). The organic layer was dried (Na₂SO₄), filtered, and concentrated *in vacuo* to an oil. The residue was purified via column chromatography

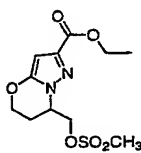
(10% EtOAc/hex then 25% EtOAc/hex) to furnish the alkylated product A (345 mg, 48% yield). 211.1 (M+H), ret. t: 3.49 min (A).

- 5 B. 6,7-Dihydro-7-(hydroxymethyl)-5H-pyrazolo[5,1-b][1,3]oxazine-2-carboxylic acid ethyl ester



To a solution of the compound from step A (100 mg, 0.479 mmol) in CH₂Cl₂ (1 mL) at 0°C was added m-CPBA (165 mg, 0.958 mmol), and the reaction mixture was allowed to warm to RT slowly. The reaction was stirred for 24h and the diluted with CH₂Cl₂ (50 mL) and washed with dilute NaHCO₃ (1x20 mL). The aqueous layer was further extracted with CH₂Cl₂ (2x25 mL). The combined organic extracts were dried (Na₂SO₄), filtered, and concentrated *in vacuo* to an oil. The residue was purified via column chromatography (33% EtOAc/hex then 75% EtOAc/hex) to furnish the above compound B (56 mg, 52% yield). 227.1 (M+H), ret. t: 2.48 min (A).

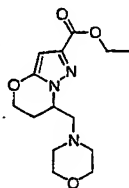
- 20 C. 6,7-Dihydro-7-[[[(methanesulfonyl)oxy]methyl]-5H-pyrazolo[5,1-b][1,3]oxazine-2-carboxylic acid ethyl ester



To a solution of the compound from step B (69 mg, 0.31 mmol) in CH₂Cl₂ (2 mL) was added methanesulfonyl chloride (0.036 mL, 0.46 mmol) and TEA (0.11 mL, 0.76 mmol), and the reaction mixture was stirred for 2h. The reaction mixture was poured into CH₂Cl₂ (25 mL), washed with water (20 mL) and dried (Na₂SO₄). The organic extract was filtered and concentrated *in vacuo* to furnish the above crude ethyl ester C (92 mg, 99% yield). 305 (M+H), ret. t: 1.10 min (B).

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- D. 6,7-Dihydro-7-(4-morpholinylmethyl)-5H-pyrazolo[5,1-b][1,3]oxazine-2-carboxylic acid ethyl ester

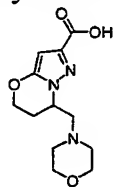


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To the compound from step C (95 mg, 0.31 mmol) in dry THF (0.5 mL) was added morpholine (0.133 mL, 1.52 mmol) and the reaction was heated at reflux overnight. The reaction mixture was concentrated and purified directly by column chromatography (50% EtOAc/hex then 2% MeOH/CH₂Cl₂) to afford the above compound D (83 mg, 93% yield). 296.3 (M+H).

10

- E. 6,7-Dihydro-7-(4-morpholinylmethyl)-5H-pyrazolo[5,1-b][1,3]oxazine-2-carboxylic acid



15

To a solution of the ester from step D (83 mg, 0.28 mmol) in MeOH (0.6 mL) was added 3N NaOH (0.2 mL), and the reaction mixture was heated at reflux for 40 min. The reaction was cooled to RT and stirred overnight. The crude acid was purified via column chromatography (5% MeOH/CH₂Cl₂ then 20% MeOH/CHCl₃ saturated with NH₃). The product fractions were collected and concentrated with water three times to give the above-titled free acid E (94 mg, 99% yield), ret. t: 0.93 min (A).

20

- F. 6,7-Dihydro-7-(4-morpholinylmethyl)-N-[(1S,2S)-1,3,3-trimethylbicyclo[2.2.1]heptan-2-yl]-5H-pyrazolo[5,1-b][1,3]oxazine-2-carboxamide

25

The acid of step E was converted to the above-titled carboxamide using the general procedure described above for Examples 17-66. 403.3 (M+H), ret. t: 1.73 min (B).